



University of Southern California  
Human Subjects Protection Program (HSPP)  
Policies and Procedures

Office for the Protection of Research Subjects (OPRS)

USC Institutional Review Boards (IRB)

**2018**

## Message from the USC Institutional Official

Institutions are charged with establishing policies and procedures for the protection of human research subjects according to federal policy. As the Institutional Official named in the University of Southern California (USC) Federalwide Assurances, it is my responsibility to provide and oversee these policies and procedures. These policies are regularly updated as practices and regulatory changes dictate.

The USC Human Subject Protection Policy and Procedures are designed to facilitate the protection of human subjects involved in research conducted under the auspices of the University. Investigators, IRB members and staff are encouraged to familiarize themselves with the policies and procedures and utilize them during the submission, review, and conduct of human subjects research.

Protecting the rights and welfare of human subjects is an important responsibility that can best be met through education of all parties involved in the conduct of human subject's research and implementation of practices designed to minimize risks and maximize benefits associated with these activities.

Thank you for your cooperation in our joint effort to protect the human subjects involved in our research studies.

A handwritten signature in blue ink, appearing to read 'R. W. Hall', is written over a horizontal line.

Randolph W. Hall, Ph.D.

Vice President of Research

# Statement of the University of Southern California



## CODE OF ETHICS OF THE UNIVERSITY OF SOUTHERN CALIFORNIA

At the University of Southern California, ethical behavior is predicated on two main pillars: a commitment to discharging our obligations to others in a fair and honest manner, and a commitment to respecting the rights and dignity of all persons. As faculty, staff, students, and trustees, we each bear responsibility not only for the ethics of our own behavior, but also for building USC's stature as an ethical institution.

We recognize that the fundamental relationships upon which our university is based are those between individual students and individual professors; thus, such relationships are especially sacred and deserve special care that they not be prostituted or exploited for base motives or personal gain.

When we make promises as an institution, or as individuals who are authorized to speak on behalf of USC, we keep those promises, including especially the promises expressed and implied in our Role and Mission Statement. We try to do what is right even if no one is watching us or compelling us to do the right thing.

We promptly and openly identify and disclose conflicts of interest on the part of faculty, staff, students, trustees, and the institution as a whole, and we take appropriate steps to either eliminate such conflicts or insure that they do not compromise the integrity of the individuals involved or that of the university.

We nurture an environment of mutual respect and tolerance. As members of the USC community, we treat everyone with respect and dignity, even when the values, beliefs, behavior, or background of a person or group is repugnant to us. This last is one of the bedrocks of ethical behavior at USC and the basis of civil discourse within our academic community. Because we are responsible not only for ourselves but also

for others, we speak out against hatred and bigotry whenever and wherever we find them.

We do not harass, mistreat, belittle, harm, or take unfair advantage of anyone. We do not tolerate plagiarism, lying, deliberate misrepresentation, theft, scientific fraud, cheating, invidious discrimination, or ill use of our fellow human beings – whether such persons be volunteer subjects of scientific research, peers, patients, superiors, subordinates, students, professors, trustees, parents, alumni, donors, or members of the public.

We do not misappropriate the university's resources, or resources belonging to others which are entrusted to our care, nor do we permit any such misappropriation to go unchallenged.

We are careful to distinguish between legal behavior on the one hand and ethical behavior on the other, knowing that, while the two overlap in many areas, they are at bottom quite distinct from each other. While we follow legal requirements, we must never lose sight of ethical considerations.

Because of the special bonds that bind us together as members of the Trojan Family, we have a familial duty as well as a fiduciary duty to one another. Our faculty and staff are attentive to the well-being of students and others who are entrusted to our care or who are especially vulnerable, including patients, volunteer subjects of research, and the children in our daycare and community outreach programs.

By respecting the rights and dignity of others, and by striving for fairness and honesty in our dealings with others, we create an ethical university of which we can all be proud, and which will serve as a bright beacon for all peoples in our day and in the centuries to come.

*Adopted by the Board of Trustees of the University of Southern California, March 28, 2004*

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# **PREFACE**

## **Commitment of USC to Human Subjects Protection**

At USC, protection of research subjects is a university-wide function that merits and receives the highest level of institutional support, commitment, visibility, and rigor. A vast and successful research enterprise is a catalyst for societal benefits and economic well-being. Thus, maintaining public trust in USC's academic research is a critical goal. An excellent Human Subjects Protection Program (HSPP) is a vital part of retaining this trust and assuring that priority is given to the rights and welfare of those who participate in research.

The policies, procedures, and commitment established by this document reflect the practices, expectations and standards to which this Institution adheres.

	<b>Chapter 1: USC Human Subjects Protection Program</b>
<b>Chapter Contents</b>	
1.1 – Human Subjects Protection Program (HSPP)	
1.2 – Human Subjects Protection Program Components	
1.3 – How the Organization Works Together to Protect Subjects	
1.4 – Research Involving the Community	
1.5 – Flexibility Policy	

# Chapter 1

## USC Human Subjects Protection Program

This chapter describes the purpose and composition of the USC Human Subjects Protection Program (HSPP). It also addresses how the Program protects human subjects and how USC involves the community in research. Lastly, this chapter introduces the USC Flexibility Policy.

### 1.1 Human Subjects Protection Program (HSPP)

The University of Southern California (USC) Human Subjects Protection Program (HSPP) oversees all research involving human subjects at USC. At USC, the HSPP program has the full support of the upper levels of the administration including the Board of Trustees, the President, the Provost and the Provost's staff. The members of the program include the Vice President of Research, Executive Director and staff of the Office for the Protection of Research Subjects (OPRS), and staff, Chairs, members of the USC Institutional Review Boards (IRBs).

The HSPP team is supplemented by faculty from both campuses and the Office of Compliance for guidance and issue resolution. The primary responsibility of the HSPP is to assure the protection of subjects participating in USC research and continuing to meet and exceed accreditation standards. For studies involving USC neighboring communities, USC involves the community in planning, designing and participating in the conduct of research.

The University of Southern California is committed to conduct biomedical and behavioral research involving human subjects following the ethical principles embodied in [\*The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research\*](#) found in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The USC IRBs have been established in compliance with existing regulations of the federal government under U.S. Department of Health and Human Services (DHHS) regulations in [45 CFR 46](#), the Food and Drug Administration (FDA) regulations in [21 CFR 50](#), [56](#) as well as other applicable federal regulations and state and local laws. USC

## Chapter 1: USC Human Subjects Protection Program

**complies with requirements stipulated by other federal agencies when they serve as sponsors or have oversight of research conducted at USC.** For a list of applicable federal regulations, refer to <https://oprs.usc.edu/policies-and-procedures/federal-agencies/>

The IRBs are in compliance with [International Conference on Harmonization Good Clinical Practice Consolidated Guidelines](#) insofar as those guidelines are consistent with the FDA and DHHS regulations pertaining to the protection of human subjects in research.

The USC IRBs operate with a Federalwide Assurance issued by the DHHS, Office for Human Research Protections ([OHRP](#)). The USC IRB's are registered in the OHRP/FDA IRB database.

USC has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research (by “unchecking the box”), the terms of which allow an appropriate level of flexibility for research involving no greater than minimal risk. This provides an appropriate level of administrative flexibility without compromising subject protections. Subject protections remain equivalent for all studies whether funded or not. For research involving no greater than minimal risk and receiving no federal funds, USC has created an innovative flexibility policy adapted by other Institutions nationwide.

ALL human subject research projects at USC must be reviewed and approved by an IRB before research can begin. While the principal investigator has primary responsibility for the conduct of the study, the USC IRBs are responsible for protecting the rights and welfare of study subjects under Federal Wide Assurances (FWAs) granted by DHHS (<http://www.hhs.gov/ohrp/assurances/assurances/index.html>). This fundamental commitment to the protection of human subjects applies to all USC research involving human subjects regardless of whether the research is funded through government, non-profit or industry sponsors, through University funds, or not funded at all, and regardless of the location of the research.

The University and its researchers adhere to federal, California, and local regulations and laws as appropriate. USC will comply with requirements stipulated by other federal agencies when they serve as sponsors of research conducted at USC. Ethical and procedural guidelines by recognized organizations are also used for achieving best practices.

The OPRS oversees university wide human subjects' protections through program oversight, education, policy setting, and outreach.

## **Chapter 1: USC Human Subjects Protection Program**

The IRBs at USC are delegated the authority to review all human subjects research proposals - funded or not - that are conducted by USC faculty, staff, graduate, and undergraduate students.

USC IRBs review, approve, and monitor all research involving human subjects under the jurisdiction of their FWAs. Each IRB office provides administrative support to the IRB committees, provides assistance to investigators who are preparing IRB applications, and maintains records of IRB reviews and approvals for investigators.

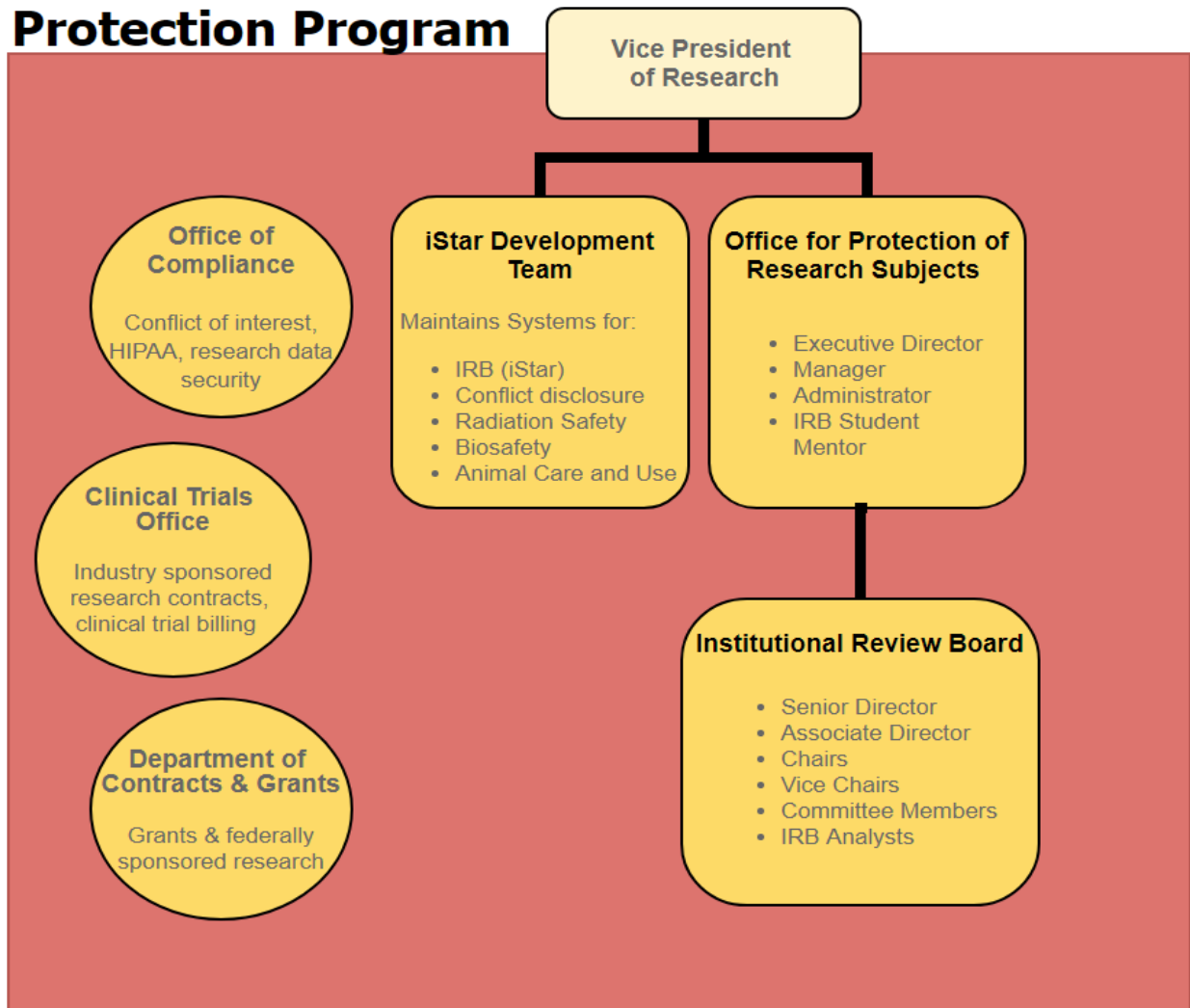
The USC IRBs are responsible for review of all biomedical and social and behavioral research conducted on the USC University Park Campus and Health Science Campus.

The Office of Compliance and/or the Office of General Counsel are available for assistance and legal counsel in applying laws to research involving human subjects.

Note: the terms “subject” and “participant” are used interchangeably throughout the Policies & Procedures.

## Human Subjects Protection Program (HSPP) Organizational Chart

### Human Subjects Protection Program



## **1.2 Human Subjects Protection Program Components**

### **Institutional Official/Human Subjects Research**

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Executive Director  
Program Director  
Program Administrator  
Graduate Assistant/IRB Student Mentor  
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E-mail: [oprs@usc.edu](mailto:oprs@usc.edu)  
Web: <https://oprs.usc.edu/>

### **Institutional Review Boards**

Senior Director  
Chairs  
Vice-Chairs  
Associate Director  
Manager  
Health Research Association Building (HRA)  
1640 Marengo Street, Suite 700  
Los Angeles, CA 90033-9269  
TEL: (323) 223-2340 FAX: (323) 224-8389  
E-mail: [irb@usc.edu](mailto:irb@usc.edu)

### iStar/Electronic Submission

Director  
3720 S. Flower Street, #325  
Los Angeles, CA 90089  
TEL: (323) 276-2238  
E-mail: [istar@usc.edu](mailto:istar@usc.edu)  
Web: <https://istar.usc.edu>

### Clinical Trials Office (CTO)

Director  
2011 N. Soto Street  
Los Angeles, CA 90032  
TEL: (323) 442-7218    FAX: (213) 342-0947  
Web: <https://research.usc.edu/clinical-trials-at-usc/>

## 1.3 How the Organization Works Together to Protect Subjects

The Human Subjects Protection Program oversees the ethical and regulatory affairs related to the protection of research subjects. The Program consists of the Vice President of Research, the Office for the Protection of Research Subjects (OPRS), four Institutional Review Boards, and the Department of Contracts and Grants. USC faculty, staff, and students are also participants in the HSPP. All these groups carry out their individual functions and endeavor to work together where their responsibilities intersect in human subjects protection.

The University's commitment to ethical and compliant human subjects research is embodied in the USC Code of Ethics, Faculty Handbook, and the HSPP Policies and Procedures.



### Office for the Protection of Research Subjects

Responsible for: promoting excellence in human subjects research programs across the University, overseeing the IRB, providing human subjects education, seeking out and adopting best practices, advising the Vice President of Research, maintaining accreditation, and providing a national voice and presence in human subjects protections.

Accountability within the HSPP is expected of all levels of responsibility.

Communication is routinely shared among all components of the HSPP. IRB members are encouraged to directly contact the IRB staff, Directors, Chairs and Vice Chairs or OPRS with questions, concerns, or suggestions. Regulatory and IRB policy changes are provided to the members and staff via email, through the OPRS listserv, and at IRB meetings. Education sessions are held for members and staff at the meetings, and for researchers' special education sessions are given on an as-needed basis.

#### Human Subjects Working Group

Human Subjects Working Group consisting of OPRS, IRB Chairs and Directors meet regularly on monthly phone calls to discuss best practices, address and solve issues, and share news or concerns that affect the HSPP. Any IRB related issues taking place on either campus can be discussed at that time.

Other meetings and phone calls take place, as necessary, to deal with any problems, issues, concerns. These calls or meetings can be initiated by any member of the HSPP team.

#### OPRS/IRB Websites

OPRS/IRB websites receive thousands of visits per month, and provide a wealth of information to all stakeholders in human subjects research. Not only is there guidance for investigators and IRB staff, there is also information for research participants/subjects. The websites are continually updated with the most recent human subjects research policies, regulations, guidance, and news.

#### Human Subjects Research Listserv

Human Subjects Research Listserv is used by OPRS to communicate with IRB staff and members, as well as USC faculty, staff and students conducting human subjects research. This listserv includes the most recent information on federal and state regulations, IRB

education opportunities at USC, human subjects news, legislation, and other pertinent human subjects research information that the USC community should be aware of.

### **Program Communication**

IRBs have weekly staff meetings to ensure that issues within that IRB can be addressed and that all staff are made aware of any new regulations or guidance that may be available. Staff problems or concerns are also addressed at this time, or can be done on an individual basis. Issues that can benefit or educate others in the HSPP are forwarded to the OPRS for discussion and distribution to the entire HSPP team.

The Executive Director of the Office for the Protection of Research Subjects and Vice President of Research meet as needed. In these meetings, issues pertaining to the HSPP are addressed as are new suggestions or decisions, needing input at the Provost level.

## **1.4 Research Involving the Community**

USC promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results. Community involvement builds public awareness and trust in research. Additionally, the more involved the community is, the more likely it is to benefit from research discoveries.

Researchers have flexibility to develop their own approach to engagement, in keeping with the needs of a particular community. However, the approach must be rooted in ethical considerations – respect for persons, equitable selection of subjects, and beneficence – and should emphasize community outreach, consultation, involvement and collaboration.

At USC, the preponderance of community-engaged research occurs in Preventive Medicine at HSC and in the School of Social Work at UPC. When appropriate, the researcher will promote the involvement of community member in the design and implementation of research and the dissemination of results.

Several initiatives have been established by the Southern California Clinical Translation Science Institute (SC-CTSI) that provide guidance for conducting community-engaged research as outlined in [A Quick Start Guide to Conducting Community-Engaged Research](#). For example, some research studies fund community activities that open the dialogue to USC research in general while also providing study-specific information.

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From such collaborations, researchers can identify community research needs and community members can identify research risks not known to researchers.

In addition to CTSI resources, the Office for the Protection of Research Subjects (OPRS) website provides information for prospective research participants about types of research being offered at USC, questions to consider before participation, and contact information for reporting research complaints and concerns. Brochures are available in English and Spanish to inform individuals in the community about what to know before participating in a research study. For additional information see references below.

### *Helpful Links*

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- OPRS Community Engaged Research webpage  
<https://oprs.usc.edu/about/initiatives/>
- OPRS Participating in Research webpage  
<http://oprs.usc.edu/about/participating/>
- SC CTSI website  
<http://sc-ctsi.org/>
- SC CTSI Community Engagement Partners  
[http://sc-ctsi.org/index.php/community/community\\_engagement\\_partners](http://sc-ctsi.org/index.php/community/community_engagement_partners)

## **1.5 Flexibility Policy**

### **Basis of Flexibility Policy**

The University of Southern California has chosen to limit the application of the federal regulations to federally funded or federally regulated research. For research projects outside the scope of the federal regulations subjects will nonetheless be afforded equivalent protections. This Flexibility Policy is limited to studies involving no greater than minimal risk as well as no federal funding.

*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests and any disclosure of the human subjects' responses outside the research would not

reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

This policy establishes flexibility in review, administration, and oversight of human subjects research. USC will also be encouraging and supporting additional opportunities for flexibility when encountered. Flex projects determined to be minimal-risk research do not require continuing review (unless specifically required by the IRB); and may still require a HIPAA waiver.

### **Implementation of Flexibility Policy**

All human subjects research projects conducted or supported at USC remain subject to USC IRB policies and review, whether they qualify for this policy or not. When questions of applicability arise, studies will be reviewed on a case by case basis.

**Inclusion/exclusion of any research project will be at the discretion of the USC Institutional Review Boards (IRBs).**

The IRB may make exceptions to this policy for funded research that is not federally funded. Studies reviewed under this policy remain subject to USC IRB policies and review.

Should a study approved under the Flexibility Policy obtain federal funding or should the risk level change, it is the responsibility of the Principal Investigator to notify the IRB and submit an amendment for the change. Under no circumstances will federally funded or FDA regulated research be reviewed under this policy. Minimal risk studies approved under the Flex Policy will require an amendment if there is a change in risk, funding, or scope.

Research projects that meet the federal definition for human subject research and exceed minimal risk are subject to the criteria for approval articulated in the regulations at 45 CFR 46 and/or FDA regulations as applicable and do not qualify for review under the flexibility policy.

A Flexibility Coalition was established by the University of Southern California to disseminate flexibility policies and encourage similar programs at academic Institutions across the United States.

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2.2 – Declaration of Helsinki	
2.3 – National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	
2.4 – Belmont Report	

# Chapter 2

## Ethics

This chapter examines the history and development of current human research subjects protections in the US by summarizing the significant ethical and regulatory documents: Nuremberg Code, Declaration of Helsinki, National Institute of Health's Policies for the Protection of Human Subjects, National Research Act, and the Belmont Report. This chapter further describes the boundaries between 'medical practice' and research and the basic principles for conducting ethical human subjects research.

### 2.1 Nuremberg Code

Modern human subjects protections began in 1948 with the [Nuremberg Code](#) developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that “the voluntary consent of the human subject is absolutely essential”. Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time.

### 2.2 Declaration of Helsinki

Recommendations similar to the Nuremberg Code were made by the World Medical Association in its initial [Declaration of Helsinki 1965](#). The current [Declaration of Helsinki 2013](#) further distinguishes therapeutic from non-therapeutic research and restrict use of placebos in clinical trials, a position not accepted by the US.

## **2.3 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission (established partly in response to outrage over the Tuskegee study funded by the U.S. Public Health Service) met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects and recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended Department of Health, Education, and Welfare (DHEW) administrative action to require that the guidelines apply to research conducted or supported by DHEW. The Commission's report set forth the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects which is titled The Belmont Report.

### **Boundaries between Practice and Research**

While recognizing that the distinction between research and therapy is often blurred, practice is described as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.”

The Commission distinguishes research as “designating an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.”

The Report recognizes that “experimental” or innovative procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such “experimental” procedures should be investigated early, and that Institutional oversight mechanisms, such as medical practice

committees, can ensure that this need is met by requiring that “major innovation(s) be incorporated into a formal research project.”

### 2.4 Belmont Report

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report titled [\*The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research\*](#). The Report sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three essential requirements for the ethical conduct of research involving human subjects.

#### Respect for Persons

**Informed consent**, required by the moral principle of respect for persons contains three elements: **information, comprehension, and voluntariness**. First, subjects must be given sufficient **information** on which to decide whether or not to participate, including the research procedure(s), purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.

Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for such persons may require that the permission of third parties also be given in order to further protect these persons from harm.

Finally, consent to participate must be **voluntarily** given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.



### Beneficence

Closely related to the principle of beneficence, risk/benefit assessments “are concerned with the probabilities and magnitudes of possible harms and anticipated benefits.” The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of the benefits for the individual, as well as reasonably achievable societal benefits.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the validity of the theory underpinning the proposed research; (2) distinguish the “nature, probability and magnitude of risk...with as much clarity as possible;” and (3) “determine whether the investigator’s estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.”

Five basic principles or rules apply when making the risk/benefit assessment: (1) “brutal or inhuman treatment of human subjects is never morally justified;” (2) “risks should be minimized, including the avoidance of using human subjects if at all possible;” (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving “significant risk of serious impairment” (direct benefit to the subject or “manifest voluntariness of the participation”), (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

### Justice

The principle of justice mandates that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The “justness” of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

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With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (involving “undesirable” persons in risky research). Further, “social justice” indicates an “order of preference in the selection of classes of subjects (adults before children) and that some classes of potential subjects (the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.”

Investigators, Institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that “arises from social, racial, sexual, and cultural biases institutionalized in society.”

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are “easy to manipulate as a result of their illness or socioeconomic condition.” Care should be taken to avoid overburdening institutionalized persons who “are already burdened in many ways by their infirmities and environments.” Non-therapeutic research that involves risk should use other, less burdened populations, unless the research “directly relate(s) to the specific conditions of the class involved.”

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## Chapter 3 Federal Regulations and State Laws

This chapter provides an overview of the federal regulations and California law that govern human subjects research at USC. These include: Health and Human Services, Defense, Justice, Energy, Education and California law. The chapter concludes with a brief discussion of California laws that impact human subjects research.

### 3.1 Department of Health and Human Services (DHHS)

#### Common Rule ([45 CFR 46](#))

In 1981, in response to the Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the FDA promulgated significant revisions of their human subjects regulations. The revisions were concerned with details of what the IRB is expected to accomplish and some of the procedures it must follow.

The DHHS regulations are codified at [Title 45 Part 46](#) of the Code of Federal Regulations. Those "basic" regulations became final on January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision became the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule," as it is sometimes called) was jointly promulgated by the sixteen federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted many of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments that adopt it. The "common" part of title 45 part 46 is also known as subpart A.

\*Additional federal agencies/departments have since adopted [45 CFR 46](#).

- [Subpart A](#), "Basic HHS Policy for Protection of Human Research Subjects", revised effective June 23, 2005.

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Additional protections for various vulnerable populations have been adopted by DHHS in the subparts of title 45 Part 46 as:

- [Subpart B](#), “Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human In vitro Fertilization” revised effective November 2001.
- [Subpart C](#), “Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects” became final on November 16, 1978.
- [Subpart D](#), “Additional Protections for Children Involved as Subjects in Research” became final on March 8, 1983, and was revised for a technical amendment on June 18, 1991.

### FDA (21 PARTS 50 AND 56)

Food and Drug Administration (FDA) regulations on the protection of human subjects are codified at [Title 21 Parts 50](#) and [56](#) of the Code of Federal Regulations. **Part 50**, which sets forth the requirements for informed consent. Subpart C provides special protections for prisoners. Subpart D provides Additional Safeguards for Children in Clinical Investigations. **Part 56** sets forth the provisions for Institutional Review Boards.

Additional FDA regulations that are relevant to IRB review of research are **Parts 312** (Investigational New Drug Application), [600](#) (Biological products), [812](#) (Investigational Device Exemptions) and [860](#) (Medical Device Classification Procedures).

For a comparison of FDA and HHS Human Subject Protection Regulations, click [here](#).

For additional information about FDA-regulated research, refer to [Chapter 18 – FDA-Regulated Research](#).

### HIPAA (45 PARTS 160 AND 164)

The HIPAA Privacy Rule is under the jurisdiction of the Office of Civil Rights which is responsible for interpreting, establishing guidelines, and any subsequent modifications of the rule. Information regarding the most recent version of the Privacy Rule - Health Information Technology for Economic and Clinical Health (HITECH Act), may be found at: <http://www.hhs.gov/about/news/2013/01/17/new-rule-protects-patient-privacy-secures-health-information.html>

### 3.2 Department of Defense (DOD) and Department of the Navy (DON)

The Department of the Navy (DoN) supports research involving human subjects conducted by a non-DoD institution by way of contracts, grants, assistance agreements, cooperative agreements, cooperative research and development agreements and other partnering agreements. As of February 1st, 2016, DoN no longer required or issued the Navy Addendum to the FWA. DoN implements human research protection requirements through the Common Rule (32 CFR 219), Department of Defense Instructions ([DoDI 3216.02](#)) and directives, and DoN instructions ([SECNAVINST 3900.39D](#)). The DoD and DoN also have additional requirements for research involving human subjects, including the requirement for review by a Human Research Protection Official (HRPO). Resources and guidance may be found at the following website: <https://www.health.mil/Military-Health-Topics/Privacy-and-Civil-Liberties/Protect-Humans-in-Research/HRPO-Review-of-Research-Protocols>

Researchers should be cognizant that DOD requirements may lead to additional costs related to the conduct of the study.

Researchers are urged to anticipate any specific subject protection costs that might be directly associated with the DOD project. For example, if a project poses greater-than-minimal risk and therefore requires a Research Monitor, costs associated with the monitor might qualify as direct costs. For assistance in identifying such costs and dealing with the funding agency, please consult with the USC Office of Contracts & Grants for assistance.

Note: If you are designing a project that will involve other entities as collaborators or sub-contractors, you are strongly encouraged to consult with the DOD or the sponsor to identify additional requirements.

#### Research Supported by the Department of Defense (DOD)

When submitting a study to the USC IRB that is supported by or in collaboration with DOD, specific additional information must be included in the iStar application. In addition to IRB requirements, federal regulations, state laws and institutional policies, the DOD (including the Navy, Army, Air Force, and Personnel and Readiness) requires the Institution to:

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- Conduct initial and continuing research ethics education for personnel who are engaged in human subject research (who review, approve, oversee, or manage research)
- Document determination by a designated staff person (other than investigators) whether research meets criteria for exemption
- Ensure new research and substantive scientific amendments to approved research shall undergo scientific review and that the review is considered by the IRB
- Ensure additional protections for military research subjects to minimize undue influence
- Explain to subjects any provisions for medical care for research-related injury
- Report unanticipated problems, adverse events, research-related injury, and suspensions or terminations of research within 30 days from the determination that the event is reportable
- Appoint a Research Monitor when necessary
- Safeguard for research conducted with international populations
- Protect pregnant women, prisoners, and children
- Comply with DOD limitations and modifications to research with pregnant women, fetuses and neonates. Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart B with limitations and modifications:
  - For the purposes of applying Subpart B risk-benefit analysis, DOD replaces the phrase “biomedical knowledge” with “generalizable knowledge”
  - The DOD limits the applicability of Subpart B to research involving:
    - Pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or fetus; or

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- Fetuses or neonates as participants
- Fetal research must comply with the [US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g](#).
- Include women and minorities as subjects, if study is a clinical investigation including Armed Services personnel
- Comply with DOD limitations on research where consent by legally authorized representatives is proposed
- Comply with DOD limitation on exceptions from informed consent (10 USC 980, 45 CFR 46, and 21 CFR 50)
- Comply with limitations on dual compensation for U. S. military personnel
- Follow DOD requirements for additional review for DOD-sponsored survey research or survey research within DOD
- Address and report allegations of non-compliance with human research protections
- Address and report allegations of research misconduct
- Follow procedures for addressing financial and other conflicts of interest
- Prohibit research with prisoners of war (POW) and detainees
- Comply with all provisions for research with human subjects using investigational test articles (drugs, device, and biologics)
- Follow recordkeeping requirements
- Support oversight by the sponsoring DOD Component (which may include DOD Component review of the research and site visits)

An explanation of some of the additional requirements follows:



### Researcher Responsibilities

To ensure the DOD component conducts an administrative review, PIs are responsible for submitting documentation to the DOD Human Research Protection Official (HRPO) prior to starting a USC IRB-approved study.

Additionally, the following shall be reported promptly (within 30 days) to the DoD Human Research Protection Official:

- Significant changes to the research protocol approved by the IRB
- Results of the IRB continuing review
- Change of reviewing IRB
- Notification by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol
- Any suspension or termination of DoD-supported research

### Potential for Undue Influence

The military structure expects loyalty and participation and thus has the potential to unduly influence a prospective subject's decision about whether to participate in research. Commanding Officers (CO) should be alert to the potential for undue influence in research with those in employer-employee status (worker), teacher-student, supervisor-subordinate relationships, or deployed active duty personnel. Regardless of the risk level of the research, no superiors (civilian supervisors, officers, and noncommissioned officers (NCOs)) shall influence the decisions of their subordinates (junior enlisted personnel) whether to participate as research subjects.

### “Minimal Risk” Interpretation

The phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” in the definition of minimal risk should not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

### **Research Monitor**

A research monitor is required for all research involving greater than minimal risk. The IRB may determine that a research monitor is appropriate for other research. A research monitor has the authority to stop a research study, remove individuals from a study, observe group recruitment, and take whatever steps are necessary to protect the safety and well-being of participants. The IRB must approve the research monitor by name and a written summary of the monitors' duties, authorities, and responsibilities. When a research monitor is required, consult with the IRB Chair.

### **Research Related Injury Compensation**

Every research protocol involving greater than minimal risk shall provide an arrangement for emergency treatment and necessary follow-up of any research-related injuries to subjects. IRBs will determine whether research involving minimal risk also might include a similar arrangement for research-related injury. Subjects should be informed about how the costs for research related injuries will be covered.

### **Waiver of Informed Consent Prohibited**

If the research involves an intervention or interaction with subjects a waiver of consent or parental permission is prohibited unless a waiver is obtained from the Secretary of Defense.

### **International Research**

If the research involves human subjects who are not US citizens or DOD personnel, it is conducted outside the United States, and its territories and possessions additional DOD requirements must be met.

### **Military and Civilian Personnel in Research**

Civilian personnel may experience "pay check" vulnerability when research is conducted in the workplace. In addition, research findings may have unintended consequences for military and civilian personnel, such as loss of job, career, or benefits. Those involved in the research enterprise must recognize that non-participation may have subtle consequences and make every effort to avoid even the appearance of undue influence or coercion.

### **“Minors” in the Military**

Individuals may join the military with parental permission when they are less than the state-mandated age of majority (generally 18 years). However, military members who are considered minors under state law must have parental permission, in addition to their assent, to participate in research.

### **Research with Data, Documents, Records, and Specimens**

Access to data, documents, records, and specimens for research purposes requires IRB review. Examples include: mishap reports, blood specimens, training records, medical records, performance evaluations, employee records, fitness results, diving records.

### **Women in the Military**

Federal regulations encourage women of childbearing potential to participate in drug development trials, but require additional safeguards.

### **State Laws**

Military commands must comply with relevant state laws.

### **Research with Investigational Agents (Drugs, Devices, and Biologics)**

In addition to complying with DOD/DON regulations for research on investigational drugs, devices, and biologics, investigators must also adhere to the Food and Drug Administration regulations (21 CFR Part 56 - IRBs and 21 CFR Part 50 - Informed Consent). The FDA and DOD regulations on basic requirements for IRBs and for informed consent generally are consistent.

### **Prisoners in Research (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart C with limitations and modifications:

- For research intended to enroll prisoners, the DOD does not allow review by expedited mechanism.
- If a PI attests that it is in the best interest of a subject who becomes a prisoner to continue participation in the research, the DOD allows the IRB Chair to make a

preliminary determination until the convened IRB (and DOD Component, if applicable) can review the request. Otherwise, the IRB may require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB with consultation from the prisoner representative, can review this request to ensure that the rights and well-being of the human subject, now a prisoner, are not in jeopardy.

If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue.

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart D with the following modification:

- The DOD does not apply Subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DOD supported research.

### **Research Supported by the Department of the Navy (DON)**

Studies that are supported by (or done in collaboration with) the Department of the Navy (DON) are subject to requirements in addition to those imposed by the Department of Defense as described below.

#### **Researcher Responsibilities**

PIs are responsible for submitting documentation to DON prior to starting an IRB-approved study and upon subsequent reviews by the IRB (amendments, continuing reviews). DON uses such documentation to conduct a "headquarters-level administrative review."

Investigators should always report any serious adverse events, noncompliance, unanticipated problems involving risks to subjects or others, and protocol deviations and actions taken regarding the reports to the DON.

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Two DON components have documentation requirements. See the following links for the documentation requirements of each (note that the requirements differ):

- [Office of Naval Research \(ONR\)](#)
- [Department of the Navy Human Research Protections Program \(DON HRPP\)](#)

### **IRB Reporting Requirements**

The IRB may be required to notify DON and the sponsor (if there is a non-DON sponsor) of serious adverse events, noncompliance, unanticipated problems involving risks to subjects or others, and protocol deviations and actions taken regarding the reports.

The DON must be notified of any audits, investigations or inspections of DON-supported research. IRB will report such inspections to DON only when the IRB conduct or are aware of the inspection.

DON HRPP requires certain IRB documentation to be submitted that is not maintained by the PI (such as IRB meeting minutes). The IRB will provide the PI with a copy of this documentation, and it is the PI's responsibility to provide this information to the DON HRPP directly.

The contact information for submission to ONR is provided at the ONR website above. The contact information for submission to the DON HRPP is:

Department of the Navy  
Office of Research Protection (M00R)  
Bureau of Medicine and Surgery  
2300 E St., NW  
Washington, DC 20372-5300  
Fax: 202-762-0976    E-Mail: [humanresearch@us.med.navy.mil](mailto:humanresearch@us.med.navy.mil)

For additional information, refer to [Appendix E – Requirements for Department of Defense \(DOD\) Supported Research](#).

### **DON Personnel as Subjects**

DON policies do not apply when DON personnel are not the targeted subject population but incidentally participate as subjects in a project that is not supported by the DON.

### Publications

DON requires that the IRB receive and maintain copies of publications, presentations or reports based on the research protocol. Please include such items (if any) when submitting an application for continuing review or closing the study in iStar.

### Questions

If you have questions regarding Navy requirements, please contact the IRB for assistance.

### Helpful Links:

- Department of Defense Directive 3216.02: “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research”  
<http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf>
- Department of Defense Directive 3210.7: “Research Integrity and Misconduct”  
<http://www.dtic.mil/whs/directives/corres/pdf/321007p.pdf>
- Electronic Code of Federal Regulations 32 CFR 219 – Department of Defense  
[http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title32/32cfr219\\_main\\_02.tpl](http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title32/32cfr219_main_02.tpl)
- Secretary of the Navy Instruction 3900.39D, Section 4(a)(1) – Human Research Protection Program  
[http://fas.org/irp/doddir/navy/secnavinst/3900\\_39d.pdf](http://fas.org/irp/doddir/navy/secnavinst/3900_39d.pdf)

## 3.3 Department of Justice (DOJ)

When research is supported by the Department of Justice, USC fulfills its obligations with regard to the assurances and certification required by 28 CFR 46. The specific requirements for research supported by the Bureau of Prisons and National Institute of Justice are listed below.

### Research Supported by the Bureau of Prisons

#### Compliance with 28 CFR 512

USC, USC IRBs, and researchers and research staff must follow the requirements of 28 CFR 512, including:

- The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- The research design must be compatible with both the operation of prison facilities and protection of human subjects. The researcher must observe the rules of the institution or office in which the research is conducted.
- Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the provisions of 28 CFR 512.
- All research proposals will be reviewed by the Bureau Research Review Board.

#### Pilot Projects are not Considered Research

Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

#### Research Design

The project must have an adequate research design and contribute to the advancement of knowledge about corrections.

#### Subject Selection and Incentives

The selection of participants within any one organization must be equitable. Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both no longer in Bureau of Prisons custody and are participating in authorized research being conducted by Bureau employees or contractors.

### Confidentiality

A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.

Except as noted in the consent statement to the participant, the researcher must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.

Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.

If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

### Disclosure and Informed Consent

Required elements of disclosure include:

- Identification of the researchers
- Anticipated uses of the results of the research
- A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable)
- A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization



- A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility

### **Research Proposal Requirements**

When submitting a research proposal, the applicant shall provide the following information:

- A summary statement, which includes:
  - Names and current affiliations of the researchers
  - Title of the study
  - Purpose of the study
  - Location of the study
  - Methods to be employed
  - Anticipated results
  - Duration of the study
  - Number of participants (staff or inmates) required and amount of time required from each
  - Indication of risk or discomfort involved as a result of participation
- A comprehensive statement, which includes:
  - Review of related literature
  - Detailed description of the research method
  - Significance of anticipated results and their contribution to the advancement of knowledge
  - Specific resources required from the Bureau of Prisons
  - Description of all possible risks, discomforts, and benefits to individual participants or a class of participants, and a discussion of the likelihood that the risks and discomforts will actually occur
  - Description of steps taken to minimize any risks
- Description of physical or administrative procedures to be followed to:
  - Ensure the security of any individually identifiable data that are being collected for the study
  - Destroy research records or remove individual identifiers from those records when the research has been completed
- Description of any anticipated effects of the research study on organizational programs and operations
- Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules

- A statement regarding assurances and certification required by 28 CFR 46, if applicable.

### **Investigator Requirements and Responsibilities**

- The researcher must have academic preparation or experience in the area of study of the proposed research.
- The researcher must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor to the researcher.
- At least once a year, the researcher shall provide the chief, Office of Research and Evaluation, with a report on the progress of the research.
- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication, the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

### **Research Supported by the National Institute of Justice (NIJ)**

#### **Privacy Certificate**

All projects are required to have a privacy certificate approved by the NIJ Human Subjects Protection Officer. Under a privacy certificate, researchers and research staff do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting.

### Confidentiality Statement

All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.

### Disclosure and Informed Consent

The confidentiality statement on the consent form must state that confidentiality can only be broken if the participant reports immediate harm to participants or others.

### National Archive of Criminal Justice Data

A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

## 3.4 Department of Energy (DOE)

When research is supported by the Department of Energy, USC fulfills its obligations with regard to the assurances and certification required by 28 CFR 0 443.1B. The specific requirements for research supported by the Department of Energy are listed below.

### Human Subjects Research

- Research involving human participants also includes studies of the intentional modification of the human environment; generalizable includes the study of tracer chemicals, particles or other materials to characterize airflow.
- Generalizable also includes studies in occupied homes or offices that:
  - Manipulate the environment to achieve research aims
  - Test new materials
  - Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups
  - Generalizable should be viewed in terms of the contribution to knowledge within the specific field of study

### Personally Identifiable Information

Researchers are required to follow DOE requirements for the protection of personally identifiable information by completing and complying with the requirements of the [“Checklist for IRBs to Use in Verifying That HS Research Protocols Are in Compliance with DOE Requirements.”](#)

### Reporting Requirements

Researchers must promptly (**within 48 hours**) report the following to the human subject research program manager:

- Any significant adverse events, unanticipated risks, and complaints about the research, with a description of any corrective actions taken or to be taken
- Any suspension or termination of IRB approval of research
- Any significant non-compliance with HRPP procedures or other requirements
- Any compromise of personally identifiable information must be reported immediately (as soon as the breach is discovered)

## 3.5 Department of Education (ED)

When research is supported by the Department of Education, USC fulfills its obligations with regard to the assurances and certification required by 34 CFR Sections 97 Subpart D (equivalent to 45 CFR Section 46 Subpart D), 24 CFR Section 356.3 and 34 CFR Section 99. The specific requirements for research supported by the Department of Education are listed below.

### Access to Instructional Materials Used in Human Subjects Research

- All instructional material – including teachers' manuals, films, tapes, or other supplementary instructional material – which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.
- Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

- Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

### 3.6 State Laws that Apply to Human Subjects Research

In addition to federal regulations [45 CFR 46](#) and Food and Drug Administration (FDA) regulations [21 CFR 50](#), [56](#), researchers are also expected to follow state and local laws. In California, there are additional state laws applicable to human subjects research. It is the responsibility of the Institution and researchers to know and follow these laws. Visit the [Official California Legislative Information](#) website to access California Codes.

Investigators and IRB personnel with questions regarding how state or federal regulations apply to a specific research project should contact the Chair of the IRB and/or the Office of Compliance. Additional options include seeking guidance or interpretation from the USC Office of General Counsel. Final interpretation and expectations with respect to California law reside with the Office of Compliance, and Office of General Counsel at USC.

The California Protection of Human Subjects in Medical Experimentation Act ([Section 24170-24179.5](#)) requires all medical experimentation to be “undertaken with due respect for human life and the right of individuals to determine what is done to their own bodies”.

A “medical experiment” is defined (section 24174 California Health and Safety Code) as follows:

- The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, as defined in Section 109920 or 109925, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the subject or otherwise directly benefiting the subject
- The investigational use of a drug or device as provided in Sections 111590 and 111595

### Chapter 3: Federal Regulations and State Laws

- Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject

All subjects participating in a medical experiment must be provided a written “experimental subject’s bill of rights” in addition to informed consent. Refer to [Section 10.11 – California Experimental Subject’s Bill of Rights](#) for additional information.

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## Chapter 4

# Federalwide Assurances/Engagement in Research/Reliance Agreements

This chapter describes the University of Southern California (USC) Federalwide Assurances of compliance maintained with the Office for Human Research Protections (OHRP)/Department of Health and Human Services (DHHS), the definition and responsibilities of “engagement” in research and the reliance agreements related to multi-site and collaborative research.

### 4.1 Federalwide Assurance (FWA)

The following describes the University of Southern California (USC) Federalwide Assurances of compliance maintained with the Office for Human Research Protections (OHRP)/Department of Health and Human Services (DHHS). The University is required to enter into this agreement because it receives federal funding for research involving human subjects.

A Federalwide Assurance (FWA) is a binding written agreement between USC and OHRP. It states that the University will comply with federal regulations 45 Code of Federal Regulations Part 46, or simply 45 CFR 46 for all federally funded human subjects research. (See [Appendix A](#)).

USC complies with requirements stipulated by other federal agencies when they serve as sponsors or have oversight of research conducted at USC. For a list of applicable federal regulations, refer to: <https://oprs.usc.edu/policies-and-procedures/federal-agencies/>

The USC IRBs are registered in the OHRP/FDA IRB database.

### Specific FWA Requirements

FWA requirements must be met before OHRP/FWA is issued. These requirements pertain to the Institution, the institutional official, and the IRBs:



## Chapter 4: Federalwide Assurances / Engagement in Research / Reliance Agreements

- The FWA applies to all federally funded research in which USC is engaged. Refer to [Section 4.5 – Engagement in Research](#)
- The FWA requires compliance with the Federal Policy for Protection of Human Subjects ([45 CFR 46](#))
- The USC IRBs have written procedures for reporting unanticipated problems involving risks to subjects or others, serious or continuing noncompliance with federal regulations or IRB requirements and suspension or termination of IRB approval. USC must also ensure that a qualified person or persons determine research is exempt from IRB review. Finally, the USC IRBs have clear written procedures for conducting IRB initial and continuing review; approving research; reporting IRB findings to the investigator and Institution; determining which projects require review more than annually; how the IRBs ensure that changes to ongoing research are reported promptly and are not initiated without IRB review and approval (except when necessary to eliminate apparent immediate hazards to subjects)
- The FWA grants authority to the IRBs to approve, require modifications to or disapprove covered human subject research
- The FWA expects detailed informed consent requirements for research conducted under the auspices of USC
- The FWA requires that USC secure assurances from other Institutions participating in collaborative research with University investigators when applicable
- The FWA requires that the University secure written agreements of commitment relevant to human subject protection policies and USC IRB oversight if the investigator is not an employee or agent of the University and the USC IRB agrees to review the research
- The FWA requires that the University provide the IRB with resources and professional and support staff sufficient to carry out their responsibilities under the assurance

- The FWA recommends that the Institutional Official, IRB Administrator(s) and IRB Chair(s) complete a training module detailing major responsibilities of these individuals
- The FWA recommends that the University establish educational training and oversight mechanisms to ensure that research investigators, IRB members and staff and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles, relevant federal regulations, OHRP guidance, other applicable guidance, state and local laws and University policies for the protection of human subjects
- The FWA details the conditions under which the FWA must be renewed

### Responsibilities Defined under the FWA

The Federalwide Assurance also describes the responsibilities of the Institution, the Designated Institutional Official, the Institutional Review Boards and the investigator, which are detailed below. All investigators at USC are expected to conduct research in accordance with the provisions of the Federalwide Assurance and ensure that the rights and welfare of the individuals involved are protected. Faculty members who assign or supervise research conducted by students are responsible for overseeing the research to ensure that students adequately safeguard the rights and welfare of subjects and conduct the research as approved.

#### Investigator Responsibilities

The investigator is responsible for acquiring the appropriate knowledge regarding human subject protections, ethics, federal regulations, training, and monitoring to conduct his/her proposed research. The PI must assure that key study personnel are adequately trained and knowledgeable regarding human subject protections, ethical considerations, and federal regulations applicable to the proposed research. The PI is responsible for complying with the training, monitoring, and human subject research guidance as outlined in the FWA and USC IRB policies and procedures.

#### IRB Committee Responsibilities

The IRB Committee is to review all human subjects research activities and document findings regarding ethical considerations, scientific merit, adherence to federal

regulations and IRB policies and procedures. The IRB Committee must review and monitor ongoing human subjects research for adherence to the Federal regulations and IRB policies and procedures.

### IRB Staff Responsibilities

In addition to routine IRB staff duties, the OPRS/ IRB staff will participate in ongoing auditing (refer to [Section 19.3 – Audits and Assessment](#)) and monitoring activities to assure adherence to the federal regulations. The IRB staff will participate in the revisions of the IRB policies and procedures as applicable.

### IRB Administration Responsibilities

All information provided under Federalwide Assurances must be updated at least every five years, even if no changes have occurred, in order to maintain an active Assurance approved by OHRP. Amendments to the Assurance are to be reported promptly to OHRP. This includes changes to IRB Chair/Vice Chair, or a legally recognized entity of USC. USC will maintain policies and procedures reflecting the current practices of the IRB in conducting reviews and approvals under its Assurance. These policies and procedures will be maintained and kept current by the USC OPRS. They will be reviewed and revised as needed at least every three years. Changes in policy are to be finalized by the Executive Director of OPRS.

The IRB's budget will be reviewed annually, by the Executive Director of OPRS, and the Vice President of Research and modified, as necessary, to accommodate the volume and type of research reviewed, education, space, facilities, and staff.

## 4.2 Engagement in Research

The USC IRBs define engagement in research according to [OHRP's 2008 guidance](#) on the engagement of Institutions in research and [OHRP's 2011 Correspondence on "Non-Engaged Scenarios"](#).

An Institution becomes “engaged” in human subjects research when its employees or agents (all individuals performing institutionally-designated activities or exercising institutionally-delegated authority or responsibility, including faculty and students):

- Intervene or interact with living individuals for research purposes

- Obtain individually identifiable private information for research purposes [[45 CFR 46.102\(d\)\(f\)](#)]
- Obtain the informed consent of human subjects

An Institution is automatically considered to be “engaged” in human subjects research whenever it receives a direct HHS award to support such research. In such cases the awardee Institution bears ultimate responsibility for protecting human subjects under the award.

**IMPORTANT NOTE:** The USC IRBs require review by a USC IRB and by the IRB(s) at other location(s) (if the other Institution is “Engaged in the Research”) regardless of funding, unless an IRB Authorization Agreement (IAA) is required or obtained.

### Engaged Research

(For examples see the [OHRP 2008 Guidance for Engaged Research](#)):

In general, Institutions are considered engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would need to hold or obtain OHRP-approved FWAs and certify IRB review and approval to HHS) when the involvement of their employees or agents in that project includes any of the following:

- Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (awardee Institutions), even where all activities involving human subjects are carried out by employees or agents of another Institution
- Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures. Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures [See scenarios B.(1), B.(2), and B.(3) in [OHRP guidance](#) for limited exceptions]

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- Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment. Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions [See scenarios B. (1) and B. (3) in [OHRP guidance](#) for limited exceptions]
- Institutions whose employees or agents interact for research purposes with any human subject of the research. Examples of interacting include engaging in protocol dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires [See scenarios B.(1), B.(2), B.(3), and B.(4) in [OHRP guidance](#) for limited exceptions]
- Institutions whose employees or agents obtain the informed consent of human subjects for the research
- Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, Institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the Institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
  - observing or recording private behavior
  - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another Institution
  - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific

individuals by the investigator(s) either directly or indirectly through coding systems. [See scenarios B.(1), B.(2), B.(3), B.(7), B.(8), B.(9), and B.(10) in [OHRP guidance](#) for limited exceptions.]

### NOT Engaged Research

(For examples see the [OHRP 2008 Guidance for Engaged Research](#)):

Institutions would be considered **not** engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is **limited to one or more** of the following. The following are scenarios describing the types of institutional involvement that would make an Institution **not** engaged in human subjects research; there may be additional such scenarios:

1. Institutions whose employees or agents perform commercial or other services for investigators provided that **all** of the following conditions also are met:
  - a. the services performed do not merit professional recognition or publication privileges
  - b. the services performed are typically performed by those Institutions for non-research purposes
  - c. the Institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol

The following are some examples, assuming the services described would not merit professional recognition or publication privileges:

- an appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for investigators as a commercial service
- a transcription company whose employees transcribes research study interviews as a commercial service
- a hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to investigators as a service

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- a radiology clinic whose employees perform chest x-rays and send the results to investigators as a service
- 2. Institutions whose employees or agents provide medical services that are dictated by the protocol and would typically be performed as part of routine clinical care and/or follow-up, are considered “not engaged” in research provided that all of the following conditions also are met:
  - a. the Institution’s employees or agents **do not** administer the study interventions being tested or evaluated under the protocol
  - b. the clinical trial-related medical services are typically provided by the Institution for clinical purposes
  - c. the Institution’s employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research
  - d. when appropriate, investigators from an Institution engaged in the research retain responsibility for:
    - i. overseeing protocol-related activities
    - ii. ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged Institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol

Note that Institutions (including private practices) not initially selected as research sites whose employees or agents administer the interventions being tested or evaluated in the study—such as administering either of two chemotherapy regimens as part of an oncology clinical trial evaluating the safety and effectiveness of the two regimens—generally would be engaged in human subjects research (see scenario B.(3) in [OHRP guidance](#) for a limited exception). If such an Institution does not have an FWA, its employees or agents may be covered by the FWA of another Institution that is engaged in the research through completion of an [Individual Investigator Agreement](#):

<http://www.hhs.gov/ohrp/register-irbs-and-obtain-fwaf/forms/individual-investigator-agreement/index.html#>

3. Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (an oncologist at the Institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that all of the following conditions also are met:
  - a. an investigator from an Institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol
  - b. the Institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research
  - c. investigators from the Institution engaged in the research retain responsibility for:
    - i. overseeing protocol-related activities
    - ii. ensuring the study interventions are administered in accordance with the IRB-approved protocol and
    - iii. ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged Institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol **and**
    - iv. an IRB designated on the engaged Institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an Institution not selected as a research site
4. Institutions whose employees or agents:
  - a. inform prospective subjects about the availability of the research



- b. provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects' consent for the research or act as representatives of the investigators
- c. provide prospective subjects with information about contacting investigators for information or enrollment and/or
- d. seek or obtain the prospective subjects' permission for investigators to contact them

An example of this would be a clinician who provides patients with literature about a research study at another Institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient's name and telephone number to investigators.

- 5. Institutions (schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another Institution. Examples would be a school that permits investigators from another Institution to conduct or distribute a research survey in the classroom; or a business that permits investigators from another Institution to recruit research subjects or to draw a blood sample at the work site for research purposes.
- 6. Institutions whose employees or agents release to investigators at Institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research. Note that in some cases the Institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the Institution releasing such information or specimens should:
  - a. ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or

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- b. if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB's determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d)

Examples of Institutions that might release identifiable private information or identifiable biological specimens to investigators at another Institution include:

- schools that release identifiable student test scores
- an HHS agency that releases identifiable records about its beneficiaries and
- medical centers that release identifiable human biological specimens

Note that, in general, the Institutions whose employees or agents **obtain** the identifiable private information or identifiable biological specimens from the releasing Institution would be engaged in human subjects research. [See scenario A. (6) in [OHRP guidance](#)]

### 7. Institutions whose employees or agents:

- a. obtain coded private information or human biological specimens from another Institution involved in the research that retains a link to individually identifying information (such as name or social security number), and
- b. are **unable** to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:
  - i. the Institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to those employees or agents under any circumstances
  - ii. the releasing Institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the Institution's employees or agents under any circumstances, or
  - iii. there are other legal requirements prohibiting the release of the key to the Institution's employees or agents

For purposes of this document, *coded* means that:

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- identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (the code), and
- a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens

Although this scenario resembles some of the language in OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens, it is important to note that OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens addresses when research involving coded private information or specimens is or is not research involving *human subjects*, as defined in 45 CFR 46.102(f) (see <http://www.hhs.gov/ohrp/policy/cdebiol.html>). As stated in Section II of the [OHRP guidance](#), the Guidance on Engagement of Institutions in Human Subjects Research should only be applied to research projects that have been determined to involve human subjects and that are not exempt under HHS regulations at 45 CFR 46.101(b).

8. Institutions whose employees or agents access or utilize individually identifiable private information **only** while visiting an Institution that is engaged in the research, provided their research activities are overseen by the IRB of the Institution that is engaged in the research.
9. Institutions whose employees or agents access or review identifiable private information for purposes of study auditing (a government agency or private company will have access to individually identifiable study data for auditing purposes).
10. Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.
11. Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

Investigators should review all information included in the [OHRP 2008 Guidance](#). For additional questions or further clarification, investigators can contact the IRB.

## IRB Approval of USC Research at a Non-USC Site

USC faculty/staff/students conduct research at other sites, both domestic and international. When USC is engaged in research with another Institution, alternative arrangements for IRB review may be established in an agreement. (see [Section 4.3 IRB Reliance Agreements](#))

If non-USC sites are engaged in research (45 CFR 46) and have their own IRB(s) or equivalent ethics board, the USC IRB expects the non-USC sites to obtain their own IRB review for research carried out at their site, unless an IRB Authorization agreement is sought or obtained.

When conducting research at a non-USC site, USC investigators are required to provide the following information in the iStar application:

- Site name and address
- Description of activities that will take place at the site
- Whether the non-USC site has an IRB
- Confirmation of the IRB's and/or equivalent authority's approval to conduct the research
- Approved informed consent form(s) and recruitment documents, if appropriate

## 4.3 IRB Reliance Agreements

An IRB reliance agreement is an arrangement in which one IRB acts as the Reviewing IRB on behalf of other institutions - referred to as Relying IRB(s). A reliance agreement defines the roles and responsibilities of each organization collaborating on a research project.

When a study is funded by U.S. Department of Health and Human Services (HHS) and National Institute of Health (NIH), additional documentation may be required in an agreement.

Reliance agreements vary in scope, terms, and terminology. Among the commonly used reliance agreements are:

- Memoranda of Understanding (MOU)
- IRB Authorization Agreements (IAA)\*
- Master Reliance Agreement (MRA)
- Collaborative Review Agreement (CRA)
- Single IRB (sIRB) Reliance Agreement
- Central IRB Agreement (e.g. NCI's CIRB)

For a list of current USC agreements with other Institutions, refer to:

<https://oprs.usc.edu/about/initiatives/irb-review-agreements/>. Refer also to [Appendix C](#).

### USC As Reviewing IRB

The Reviewing IRB acts as the “IRB of Record” by performing the review of human subjects research for the institutions/organization involved in the reliance agreement. The responsibilities of reviewing IRB and relying sites are detailed in the reliance agreement. The agreement will include the applicable responsibilities listed below and any applicable requirements set forth by AAHRPP in Standard I-9.

When an agreement is required an IRB application must be completed.

### Responsibilities of the Reviewing IRB

- Review of initial submission, continuing review and review amendments and reportable events for all sites
- Ensure IRB approval criteria are satisfied by all participating sites, including local context information provided by relying institutions
- Review consent forms, when applicable
- Make Privacy Board determinations per HIPAA, when applicable
- Consider conflict of interest determinations, including any management plans,

relating to the research and ensure plans are incorporated into IRB review as applicable

- Notify PI, Sponsor, and federal agencies, as appropriate of IRB decisions and action, and ensure appropriate communication plan for dissemination between sites
- Maintain appropriate IRB records and documents relating to the IRB review, and make records available to relying institutions, upon request
- Notify the relying institutions of any of the following, as relevant:
  - Serious and/or continuing noncompliance, suspensions, and/or terminations
  - Audits, including findings and corrective actions
  - Reporting to a federal agency
  - Communication with regulatory agencies
- Provide relevant minutes of IRB meetings to the relying institution/organization upon request.

### Relying IRB

A Relying IRB defers to a review and approval of human research provided by an IRB that is unaffiliated with the institution. The responsibilities of the Relying IRB and the Reviewing IRB must be documented in an agreement. The agreement will include the applicable essential requirements set forth by AAHRPP Standard I-9.

The Relying IRB reviews and approves local ancillary services and is responsible for local institution-specific compliance issues.

### Responsibilities of the Relying

- Ensure research personnel are appropriately qualified and meet relying institution standards for eligibility to conduct research, including but not limited to human subjects protection training and collection and maintenance of conflict of interest disclosure forms
- Provide local context information to the reviewing IRB and ensure required information is incorporated into IRB-approved documents

- Provide local ancillary approvals to the reviewing IRB
- Ensure research personnel are notified of their responsibilities when conducting research pursuant to a reliance agreement
- Ensure compliance with the reviewing IRB determinations and requirements, applicable federal regulations, and all applicable state and local laws and institutional requirements
- Ensure appropriate monitoring of research and perform reviewing IRB-directed audits upon request
- Establish a process for reviewing conflicts of interest and creating management plans when appropriate
- Document and notify the reviewing IRB of any of the following which relates to research:
  - PI and personnel changes
  - Changes that require ICF and HIPAA revision
  - Serious and/or continuing noncompliance
  - Restriction/suspension of research activities
  - Audits, including findings and corrective actions
  - Communication with regulatory agencies
  - Legal claims
  - Research misconduct
- Receive notifications of issues from the reviewing IRB and take additional local action, if applicable

### **USC Investigator Responsibilities When Relying on An External IRB**

A USC investigator who is engaged in research and relying on an independent or external IRB must submit a Ceded Review application in iStar (iStar item 1.1). Refer to [4.2 Engagement in Research](#). The submission must include all required ancillary committee reviews (e.g., Radiation Safety).

Once the reviewing IRB approval has been obtained, the study team will upload to iStar, or provide access to, relevant study documents approved by the reviewing IRB, in order to permit completion of the USC Ceded Review process.

An acknowledgment letter will be issued by the USC IRB indicating that the study has been cleared to begin at USC.

### **IRB Reliance Agreements With USC**

A description of the most commonly used agreements are provided below.

#### **IRB Authorization Agreement (IAA)**

An IRB Authorization Agreement\* is one type of IRB reliance agreement typically used between just two institutions. It is recommended when several non-USC sites, with or without their own IRBs, rely on USC's IRB, or vice versa. The IRB Authorization Agreement may be written to cover one research project, several research projects on a case-by-case basis, or to cover a program of research.

\*Under the USC Flexibility Policy an IRB Authorization Agreement is not required if the research is not federally funded and is not subject to FDA regulations, unless the outside Institution requests an Agreement. If requested by the outside Institution, USC will comply with the request. Additionally, USC may require an IRB Authorization Agreement at its discretion.

#### **Establishing an IRB Authorization Agreement**

IRB submissions for establishing an IRB Authorization Agreement must include the research sites external to USC or CHLA. Submit an application for "Research Protocol or Study on Human Subject" (iStar item 1.1) and include any site not affiliated with USC or CHLA where research will be conducted. When ceding review and approval to an external IRB select "Ceded Review" (iStar item 1.1).

IRB Directors are authorized to sign IRB authorization agreements (subject to limitations defined by university policy. ([Provost Signature Authorization](#)))



### NIH Single IRB (sIRB) Mandate

NIH funded research that is carried out at more than one site in the United States must be overseen by a single IRB. This NIH policy applies to grant applications received on or after January 25, 2018.

The NIH policy also requires that a “communication plan” be included in grant application/proposals. The applicant/offeror is expected to submit a communication plan describing the use of an sIRB that will be selected to serve as the IRB of record for all study sites. The plan should include a statement confirming that participating sites will adhere to the sIRB policy and describe how communications between sites and sIRB will be handled. In addition, a budget for sIRB fees will be required as part of the grant application.

- [NIH Policy on the Use of a Single IRB \(sIRB\)](#)
- [Requisites for Single IRB](#)

USC IRB will act as the single IRB (sIRB) for a multi-site study of no more than 5 participating sites due to limited resources. In accordance with OHRP Guidance, an agreement must state the responsibilities of both parties. The agreement will include the applicable essential requirements set forth by AAHRPP Standard I-9.

### Cooperative (Multi-site) Research

Beginning January 2020 USC participation in any cooperative (multi-site) research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The following is the regulation 45 CFR 46.114(b) Final Revised Common Rule (January 18, 2017):

(a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects at their site and for complying with this policy.

(b)

(1) The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

- (i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or
- (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section. An institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

### **National Cancer Institute (NCI) Central IRB (CIRB)**

USC is participating in the National Cancer Institute (NCI) Central IRB (CIRB). CIRB is the IRB of Record responsible for review of the study as well as review of local context issues for participating sites. Local policy, conflict of interest, HIPAA authorization, and ancillary committee approvals are still the responsibility of the relying IRB (USC).

For research reviewed by NCI, the Clinical Investigator Support Office at USC Comprehensive Cancer Center (CISO) typically provides review of scientific merit, resources and financial aspects of the study.

### **SMART IRB**

USC is a signatory to the [SMART IRB](#) Master Reliance Agreement that is supported by NIH funding and recommended by NIH policy for single IRB review. The agreement is designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants. When possible, USC will use the SMART IRB agreement as the basis for reliance when serving as the sIRB or being a relying IRB of a SMART IRB study.

## 4.4 Transfer of IRB Oversight and Disaster Response

To prevent lapses in human subject protection, it is generally preferred, when possible, that the same IRB retain oversight responsibility throughout the conduct of a research project. Transfers may occur for a number of different reasons. The appropriate steps and considerations for oversight transfer will depend on the specific circumstances, including the reasons for the transfer and the potential risk to human subjects.

Transfer of IRB oversight may occur in any of the following circumstances, including cessation of IRB operations, consolidation of multiple IRBs into a single IRB, temporary inability of an IRB to meet its obligations, or as the result of IRB non-compliance.

If a study comes to USC with approval from a registered IRB – USC may accept the approval until the time of continuing review. If there are concerns, USC will conduct a review. If work was done under no IRB or a non-registered IRB, the study cannot be conducted until a new submission is complete and approval is provided by USC IRB.

For further guidance refer to: [“Guidance for IRBs, Clinical Investigators, and Sponsors Considerations When Transferring Clinical Investigation Oversight to Another IRB”](#)

## Disaster Response

The USC Office of Research has developed a Business Continuity Plan that contains guidance for the oversight of the functions of the USC Human Subjects Protection Program in the event of a disaster. Depending upon the breadth of a disaster, regulatory functions may be impacted. Transfer of oversight to an unaffected IRB may be required to maintain protection of human research subjects in ongoing research.

The Business Continuity Plan contains emergency response and process-specific recovery strategies for IRB functions and associated communications. Additional guidance from OHRP is available: [“Effects of Disasters on Human Research Protections Programs Guidance”](#)

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# Chapter 5

## Conflicts of Interest

This chapter describes conflicts of interest disclosures and management in relation to research. The focus is on conflict of interest specific to investigators, research team, IRB members, consultants and USC as an Institution.

USC Conflict of Interest policies reflect the U.S. Department of Health and Human Services (DHHS) and Public Health Service (PHS) [regulations effective 8/24/12](#) and the [USC Office of Compliance](#) policies.

### 5.1 Conflicts of Interest

An individual conflict of interest can arise when financial or other personal considerations compromise, or have the appearance of compromising, an individual's professional judgment in proposing, conducting, supervising, or reporting research. Conflicts can exist at the individual or institutional levels and involve financial and non-financial interests.

Conflicts of Interest may include but are not limited to the following:

- Equity (stocks or options, do not include mutual funds)
- Recruitment incentives (bonus payments) (*these are prohibited*)
- Consulting Fees
- Speaking Fees
- Travel Reimbursement
- Gifts
- Corporate Officer or Board of Directors
- Other Employment Relationship

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- Trademarks/Copyrights
- Licensing Agreements
- Royalty Payments
- Patent Holdings

An Institutional Conflict of Interest (ICOI) may occur when a financial interest of the University (investments held by the University in a company) has the potential to bias or coerce results of research conducted by its employees or students, or creates an unacceptable risk to human subjects. A Significant Institutional Conflict of Interest is deemed “significant” when a research project includes human subjects and any of the following condition applies:

- The University holds any private equity in the outside entity, or
- The University has the potential to receive cash payments from existing licensing arrangements with the outside entity, or
- The University maintains an ownership interest or an entitlement to equity in a publicly-traded sponsor of human subjects research as a result of technology licensing activities.

To address these conflicts (either individual or institutional), the university established the USC Conflict of Interest in Research Committee (CIRC) to fairly examine and manage conflicts of interest.

### **5.2 USC Conflict of Interest in Research Committee (CIRC)**

The Conflict of Interest in Research Committees (CIRC) are charged with reviewing conflict of interest disclosures and formulating recommendations to manage, reduce, or eliminate conflicts of interest. The Health Sciences Campus and University Park Campus each have their own committees. When investigators report an actual or apparent conflict of interest for a research activity, the research cannot begin until a conflict management plan has been obtained from the CIRC. Additionally, investigators are not permitted to

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begin an external activity that would create a conflict of interest relative to an ongoing research activity before they receive a conflict management plan. Investigators and research team members must comply with all the elements of the Conflict of Interest in Research Committee (CIRC) management plan. Once the CIRC determination is made and/or management plan is issued it is uploaded to the IRB application. CIRC management plans are reviewed and acknowledged by IRB members.

For full board studies, the convened IRB will document member receipt and acknowledgment or edits of the COI management plan and acknowledge. Any IRB-required changes will be noted and may be returned to the PI for action, or referred back to the CIRC for further consideration. The IRB may not limit or reduce the conditions imposed by the management plan but may impose a higher standard, if necessary, to establish that the regulatory criteria for approval of the research has been satisfied. For studies that qualify for exempt or expedited review, the COI management plan will be evaluated and acknowledged by the exempt or expedited reviewer respectively.

For COIs disclosed after full board approval of a study, subsequent CIRC review of COI and development of management plan are provided to the PI. The PI must submit an amendment in iStar and upload the management plan with any applicable changes to the study (e.g., COI disclosure in consent document). The convened IRB will document the review of the COI management plan and note any IRB-required changes, as appropriate.

At any time during the execution of a study, the disclosure of a possible COI to the CIRC results in the creation of an alert notice in iStar that identifies the study noting “A possible conflict of interest has been indicated” and or, “Possible COI has not been cleared”. For full board studies this alert creates an IRB agenda item for review of the subsequent management plan, and resolution by the original convened IRB. In the case of exempt and expedited studies, the IRB reviewer will acknowledge that the resulting management plan is acceptable.

### **5.3 Investigator and / or Research Team Conflict of Interest Disclosures**

#### **Disclosures in the IRB application (iStar)**

Potential or actual conflicts of interest must be disclosed at the time of submission of the initial and continuing review application to the IRB and at any time when the investigator and/or research team member establish a new outside relationship or change an existing relationship that creates a potential conflict of interest. Also, informed consent documents must disclose conflicts of interest, as applicable.

Conflicts of interest must be declared when the participating study investigators or other research personnel (or their immediate family/domestic partner) have an aggregated financial interest, and/or intellectual property interest in the sponsor or products used with the project, **equal to or exceeding \$5,000 per year**. Additionally, investigators must inform the IRB of monies received below \$5,000 for specific conditions defined in the iStar application. When these conditions are met, the potential conflict of interest is reviewed by the Office of Compliance.

#### **Disclosures in USC's diSClose system**

All disclosure of potential or actual conflict of interests must be made online using the [diSClose](#) system. Additionally, the IRB application includes conflict of interest questions for initial and continuing review applications. Investigators must also report conflict of interests if these arise during a study by submitting an amendment. Informed consent documents must disclose conflicts of interest, as applicable.

#### **Disclosures for Research Funded by the Health and Human Services**

Researchers who are proposing or have received HHS (including NIH, CDC, HRSA, and AHRQ) support must also make an annual disclosure of all financial interests related to their institutional responsibilities to USC, regardless of whether any of these interests give rise to a conflict of interest related to their research. The annual disclosure must be completed before a proposal can be submitted to HHS, and any identified conflicts must



be managed before an account can be established. In addition, all HHS investigators must complete training on conflicts of interest once every four years.

### Disclosures to Sponsors

Investigators must adhere to sponsor-specific disclosure requirements, as applicable.

## 5.4 Institutional Conflict of Interest (ICOI)

An institutional conflict of interest may occur when a financial interest of the University (investments held by the University in a company) has the potential to bias research conducted by its employees or students, or creates an unacceptable risk to human subjects.

All Institutional Conflict of Interests that do not present a Significant Institutional Conflict of Interest shall be managed by disclosing the University's relationship with the outside entity in all relevant publications, proposals, consent documents and presentations.

An Institutional Conflict of Interest is deemed "significant" when a research project includes human subjects and any of the following condition applies:

- The University holds any private equity in the outside entity, or
- The University has the potential to receive cash payments from existing licensing arrangements with the outside entity, or
- The University maintains an ownership interest or an entitlement to equity in a publicly-traded sponsor of human subjects research as a result of technology licensing activities.

Significant Institutional Conflicts of Interest are presumed to be unacceptable, unless compelling circumstances are present that justify allowing the research to proceed at the University despite the presence of a significant conflict. The University conducts a fact-specific inquiry to determine whether the specific circumstances of a relationship are compelling or not. For more information, refer to the [USC Institutional Conflict of Interest in Research: Policy and Procedure](#).

The Vice President of Research (VPR) will determine on a case by case basis the need for an independent IRB review of studies involving ICOI. Independent review by an outside bioethicist will provide evaluation to determine whether the ICOI meets the threshold necessary to seek review by an independent IRB.

If the VPR determines that the ICOI does not meet such criteria – the study will be reviewed by the USC IRB.

### **5.5 IRB Members and IRB Consultants Conflict of Interest**

Conflict of Interest policy considerations apply to IRB members. The IRB prohibits the participation in IRB initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

An IRB member is considered to have a Conflict of Interest if:

- The IRB member or a Close Relation of the IRB member (spouse, mutual financial dependent, significant other, or person in an intimate relationship, child, parent, or sibling (including in-laws and step-relations), grandparent, grandchild, niece or nephew, aunt or uncle, or cousin) is involved in the conduct of the research
- When the IRB member or Close Relation of the IRB member has a supervisory, managerial or ownership interest in the research sponsor, or licensee, or a company having an economic interest in the research
- Equity interest held by an IRB member or Close Relation of an IRB member in a research sponsor, or licensee, or in any company having an economic interest in the research
- Incentive payments, bonus payments or finder's fees relating to the proposal paid to the IRB member or Close Relation
- Consultation arrangements between the IRB member or Close Relation of an IRB member and an organization or individual having an economic interest in the

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research, which, when aggregated for the IRB member and the Close Relations of the IRB member, is equal to or exceeds \$5,000

- Gifts, gratuities, or special favors from the sponsor, which, when aggregated for the IRB member and the Close Relations of the IRB member, is equal to or exceeds \$5,000
- Honoraria, travel expenses reimbursement, or other reimbursements from the sponsor, which, when aggregated for the IRB member and the Close Relations of the IRB member, is equal to or exceeds \$5,000
- Intellectual property rights related to the research IRB member and the Close Relations of the IRB member
- An arrangement has been entered into where the amount of compensation/ value of ownership interests will be affected by the outcome of the research

The IRB member Conflict of Interest policy also applies to consultants. The IRB Chair or Vice Chair will be responsible for providing the consultant with a copy of the IRB member Conflict of Interest policy prior to their review of the study. Once the consultant has read the policy, the IRB Chair or Vice Chair will ask the consultant if a conflict exists. If answered in the affirmative, the consultant may not review the study. All consultants are required to maintain confidentiality and are notified of this prior to reviewing proposed research for the IRB.

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# Chapter 6

## USC Institutional Review Boards (IRBs)

This chapter describes the purpose, role, composition and general procedures of the USC Institutional Review Boards (IRBs). The USC IRBs are responsible for the review all human subjects research conducted at USC.

### 6.1 Description of USC IRBs

This chapter covers the composition of the IRB membership, the roles and requirements of IRB members, Chairs, Vice-Chairs, and reviewers at the University of Southern California (USC). Additionally, this chapter explains the use of consultants, the role of IRB staff, voting requirements, and IRB record keeping.

There are four Institutional Review Boards at the University of Southern California. The IRBs review and approve research in accordance with Department of Health and Human Services (DHHS) regulations in [45 CFR 46](#). For studies involving products regulated by the Food and Drug Administration (FDA), the University of Southern California IRBs review research and comply with the requirements set forth in [21 CFR 50](#) and [56](#), as well as [21 CFR 312](#) and [812](#). In addition, the IRBs comply with HIPAA and its regulations set forth in [45 CFR 160](#) and [164](#) and California law as it pertains to human subjects research.

USC IRBs have been delegated the following authority by the [Institutional Official](#) in his delegation [memo dated 11/23/2005](#):

- USC IRBs have the authority to approve, disapprove, or suspend human subject research projects. No USC faculty, staff, or student may conduct human subjects research without obtaining approval from the IRB
- USC IRBs have the authority to observe, or have a third party observe, the consent process and the conduct of the research.

## 6.2 The Membership of the IRB Committees

### Number, Qualifications and Diversity of Members

Each IRB has a minimum of five, but generally between eight and fifteen members with varying backgrounds to adequately review the research activities commonly conducted by the Institution. Major clinical and selected basic science departments are represented to provide the experience and expertise sufficient for review of the research activities conducted at the Institution. The IRB member with appropriate scientific expertise for each protocol will be designated to review the application. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in non-scientific areas. Also, the IRB consists of at least one member is not otherwise affiliated with the Institution and is not part of the immediate family of a person who is affiliated with the Institution.

To enable each IRB to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice, each IRB includes persons knowledgeable in these areas and may include representatives of administration. Each IRB is sufficiently qualified through the experience, expertise and diversity of its members – including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes – to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

Because the IRBs may review research that involves a vulnerable category of subjects (children, pregnant women, prisoners, and handicapped or mentally disabled persons), each IRB includes – as members or consultants as appropriate – individuals who are knowledgeable about, and experienced in, working with these categories of subjects.

Every nondiscriminatory effort will be made to ensure that each IRB does not consist entirely of men or entirely of women. The Institution will consider qualified persons of both sexes – so long as no selection is made to the IRB on the basis of gender.

### Alternate Members

When deemed necessary by the IRB Chair, and when requested by department Chairs or deans, alternates will be appointed for IRB members. Formally appointed alternate IRB members may represent IRB members, provided the alternate's qualifications are comparable to the primary member to be replaced. The IRB membership rosters identify

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the primary member(s) for whom each alternate member substitutes. Prior to the IRB meeting, materials required for review are made available electronically through iStar to all members.

The IRB minutes document when an alternate member replaces a primary member. When an alternate member substitutes for a primary member, the alternate must receive and review the same material the primary member received or would have received. Members and their alternates may not both vote. Alternates are not counted as “members” in establishing the numerical quorum of the IRB, except when they substitute for members during the IRB meeting. Alternates are invited to attend all IRB meetings, whether they are eligible to participate as voting members or not, in order to assure familiarity with the IRB practices and continuing education.

### **Ex-Officio Members**

The IRB may include ex-officio members depending on the relevance of their office and their expertise and experience. The positions they hold preclude full IRB membership and therefore ex-officio members are not voting members of the IRB.

### **IRB Student Member**

The IRB student member is a USC student selected by the Office for the Protection of Research Subjects and the IRB for outstanding commitment to the USC community, knowledge about scientific research, and legal and ethical principles guiding research involving human subjects. The IRB student member reviews IRB applications, prepares review comments, and is a full voting member of the IRB.

The IRB student member’s participation in the IRB process increases the level of student involvement in the effort to help USC research maintain the legal and ethical standards established by law and society.

## **6.3 IRB Member Requirements**

### **Selection and Appointment**

The members and alternates of the IRBs may be recommended for appointment by their Dean or Department Chair. Non-affiliate members not associated with the Institution are identified by interest and relevance and are recommended for appointment by members

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of the IRB, IRB staff, Departments or Schools. The formal appointments of IRB members are made by the Vice President of Research. Typically, individuals who are responsible for business development are not selected to serve as IRB members.

IRB committee membership lists can be found on the [OPRS](#) websites

### Length of Service

Appointments to the IRBs are for a period of 1 year. Expertise and diverse membership are expectations for both campuses. Continued tenure on the IRB is at the discretion of the IRB Chair/Director.

Evaluations of IRB composition and individual members are conducted at the end of the fiscal year at the time of IRB budget review/approval. Appointment letters indicating satisfactory evaluation of returning members are sent to IRB members at the end of one fiscal year for the next fiscal year. The duties and responsibilities of IRB members are stated in appointment letters from the Vice President of Research. Members who fail to meet IRB expectations, as outlined in the IRB appointment letters, are sent correspondence informing them that their service is no longer needed.

### Duties

Members of each IRB or their designated alternates are required to:

- Participate in agreed upon number of convened IRB meetings
- Review the IRB application and informed consent form for research proposals
- Pre-review and complete a written critique of research proposals including review of clinical trial protocol, grant application, questionnaire(s), advertisement(s), investigator's drug brochure, and informed consent form when assigned as a reviewer by the Chair, Vice Chair, or IRB staff
- Review expedited review actions of the Chair, Vice Chair, and IRB designee
- Review and promptly inform the Chair of corrections or additions to Full Board meeting minutes



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- If designated by the IRB Chairperson, review and verify that contingencies have been satisfied and further review by the IRB is not required. This does not constitute expedited review.

Selected IRB members may be appointed as expedited reviewers and can review changes to previously approved research during the period covered by the original approval. Changes that may be reviewed by an expedited reviewer are those that do not alter the original approval criteria. Additional training is provided to IRB members who are appointed to be expedited reviewers.

The IRB prohibits the participation in IRB review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Refer to [Section 5.5 – IRB Members and IRB Consultants Conflict of Interest](#) for more information.

### Attendance Requirements

Members and alternates serve at the discretion of the OPRS, IRB Chair and/or Institutional Official. Members who do not attend meetings will be removed from the IRB. If a member is unable to attend a meeting, the IRB office must be informed, sufficiently in advance, so that an alternate can be invited to attend. Frequent absences among members will be cause for removal.

### Honorarium to Non-Affiliate IRB Members

An honorarium is paid to non-affiliate IRB members based on meeting attendance. Faculty members are not paid to attend meetings.

### Liability for IRB Members

IRB members and alternates fulfill their administrative and institutional service responsibilities to the University, in part, by serving on an IRB committee. Accordingly, the University will indemnify IRB members in the event of a legal dispute relating to the actions of the committee, provided that the IRB member has acted in good faith and in accordance with federal requirements, state and local laws and University policy.

## Training of the Chair, Vice Chairs and Members

Chairs and Vice Chairs are expected to attend professional conferences (including PRIM&R conferences) to enhance their education and IRB expertise. IRB members and alternates are initially trained as guests (non-voting capacity) of the IRBs, and also offered support to attend appropriate courses, and local or national meetings. Ongoing education of the IRB membership includes an education session preceding an IRB meeting approximately once per month. In addition, access to educational materials is provided to all IRB members (such as “IRB: A Review of Human Subjects Research”). IRB members and alternates are required to take the Protection of Human Subjects education modules provided online through the CITI website <https://www.citiprogram.org/>.

## Evaluation of IRB Members

- The duties and responsibilities of IRB members will be stated in appointment letters from the Vice President of Research. Expectations and subsequent evaluation of IRB members follow: IRB members will be re-appointed annually if expectations are met. The re-appointment letter will acknowledge that the IRB member has been evaluated and satisfied the membership criteria described in HSPP policy and as provided in the appointment letter.
- For any member who fails to meet the expectations outlined in the IRB appointment letter correspondence will be sent informing them their service is no longer needed.

The IRB members will be informally evaluated annually by the IRB Chair and Director. During the evaluation, the following areas will be considered when applicable:

- Knowledge and application of federal regulations and ethical principles
- Knowledge and application of IRB policies and procedures
- Constructive participation in IRB discussion
- Attendance (notifies staff when confirming or declining to attend meetings)
- Participates in educational sessions/completes required member training
- Reviews projects as requested in a timely, comprehensive, knowledgeable manner and resolves as many issues with the investigator as possible, prior to meetings

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- Reviews all IRB application materials, meeting minutes, and expedited actions

The IRB Chairs/vice Chairs are informally evaluated by the Vice President of Research, and the OPRS on an annual basis. They are evaluated on how well they manage IRB meetings, attendance, knowledge of federal regulations and state laws, collegiality with fellow members, IRB staff, and their review (quality / quantity / timeliness) of IRB applications.

### 6.4 IRB Use of Consultants

Each IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond, or in addition to, that available on the IRB. These consultants are not counted as “members” in establishing the numerical quorum for each IRB and may not vote with the IRB. An honorarium for consultants may be provided at the discretion of the IRB Chair and/or the IRB Director.

If it is determined that a consultant is needed for the review of a protocol, the IRB Chair or Vice Chair will ask the IRB members and colleagues to refer them to individuals that would have experience with the specific type of research being reviewed. The consultants will be provided with the same information that the primary and secondary reviewers receive.

The IRB member Conflict of Interest policy also applies to consultants. The IRB prohibits the participation in IRB review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Refer to [Section 5.5 – IRB Members and IRB Consultants Conflict of Interest](#) for more information.

Copies of the consultant review are supplied to the IRB members. Consultant(s) may be asked to attend the meeting for further clarification, if deemed necessary by the IRB Chair or Vice Chair. Key information from the consultant will be included in the IRB meeting minutes and a copy of all documentation will be kept in the study file.

### 6.5 IRB Support Staff

The IRB support staff assists the Chair and Vice Chairs in IRB activities. The support staff is responsible for submitting written correspondence to investigators regarding IRB actions. IRB staff shall document meeting minutes in accordance with federal regulations and guidance. Required documents are listed in [Section 6.8 – IRB Records](#).

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IRB staff training may be provided by the IRB Director, OPRS, or IRB Chair. Staff member training also includes taking the CITI education courses, familiarity with federal, state, and local regulations, and institutional the policies and procedures. A Bachelor's Degree or prior IRB experience is required. Annual reviews are conducted to evaluate IRB staff.

The IRB staff will be evaluated annually, at the time of budget reviews, by the IRB Chair/Director. The following criteria: knowledge of the IRB process and regulations, continuing training, work attendance, and, overall ability to function as an asset to the IRB, will be measured. If a staff member is found to be deficient in a particular area or areas, they will be further educated on the IRB process. If gross errors have been uncovered, further actions, as described in University policies will be taken. The evaluation will be reflected in the annual salary determination.

### **IRB Support Staff Duties:**

- Screen submissions before IRB review
- Prepare IRB meeting agenda
- Prepare meeting minutes (see [“Meeting Minutes” in Section 6.8 – IRB Records](#))
- Prepare correspondence
- Facilitate review of IRB applications
- Customer service
- Database and information management
- Train student mentors
- Respond to subject concerns
- Follow office procedures
- Follow IRB policy and procedures and make suggestions/recommendations
- Undertake and provide education and training
- Intra-institutional relationships
- Handle meeting logistics

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- Review and approve non-material contingencies such as those related to personnel changes (excluding change of PI), punctuation and wording or verification that something missing has been supplied
- Preliminary review of initial/continuing review documents (confirm all required documents have been submitted by the investigator, confirm the consent document submitted by investigator matches the one on file, identify issues and concerns for IRB consideration)

Selected IRB staff may be appointed as IRB members (or alternate members). Additional training is provided to IRB staff who are also IRB members.

### 6.6 IRB Chairs and Vice Chairs

#### Chairperson

##### Selection and Appointment

The Chair is selected from among the faculty of the Institution and appointed by the Institutional Official. The Chair should have previously served as a member of the IRB.

##### Selection Criteria

The criteria used to select a Chair include experience with, and knowledge of, applicable federal regulations, state laws, and Institutional policies. They must be willing to commit their service to the IRB; must have past experience as an IRB member; and must demonstrate excellent communication skills, along with an understanding of clinical research. They must also demonstrate a thorough understanding of ethical issues involved in clinical/social behavioral research.

##### Length of Term/Service

The term of appointment of the Chair is determined by the Institutional Official in consultation with the Executive Director of the Office for the Protection of Research Subjects.

##### Attendance Requirements

The Chair is required to attend the majority of the convened IRB meetings.

### Duties

The Chair of the IRB convenes and chairs the meetings of the IRB. The Chair may conduct or delegate expedited review of research that qualifies as expedited, review the responses of investigators to contingencies in expedited studies or studies that qualify for the expedited procedure. The Chair/IRB designee reviews and approves expeditable amendments in previously approved research, unless the change affects the approval criteria. The Chair/IRB designee may approve a Waiver of HIPAA Authorization for research that meets specific criteria outlined in [USC Administrative and Business Practices Policy / Compliance / HIPAA](#).

### Project Referrals

The Chair may, at their discretion, refer the review of a research project to the IRB of the other campus if it is determined that more appropriate expertise lies in the other IRB.

## Vice Chairpersons

### Selection and Appointment

Vice Chairs are selected from among the faculty at the Institution and are appointed by the Institutional Official (the Vice President of Research) in consultation with the Chairs / IRB Director and Executive Director of the Office for the Protection of Research Subjects. The Vice Chairs must have previously served as members of the IRB.

### Length of Service

The term of appointment of the Vice Chair is determined by the Institutional Official in consultation with the Chairs / IRB Director and the Executive Director of the Office for the Protection of Research Subjects.

### Attendance Requirements

Vice Chair will be assigned to Chair an IRB meeting when the Chair is unable to conduct the meeting.

### Duties

The Vice Chairs of the IRB are designated by the Chair to carry out expedited review of research that qualifies for such review. The Vice Chairs shall be authorized by the Chair to review the responses of investigators to contingencies of the IRB (to secure IRB

## **Chapter 6: USC Institutional Review Boards (IRBs)**

approval) and to review minor changes in previously approved research during the period covered by the original approval. The Chair, Vice Chairs, IRB Director, or IRB staff assigns the primary reviewers to pre-review new research proposals submitted to the IRB for consideration at the Full Board meetings.

### **6.7 IRB Voting Requirements**

Reviews of proposed research are conducted at a convened IRB meeting at which a majority of the members are present. At least one IRB member whose primary concerns are in non-scientific areas, one member whose primary concerns are in scientific areas, and one non-affiliate member must be present. In the event a majority of members are not present, or there is no member whose primary concerns are non-scientific, or a non-affiliate member is not present, the meeting will not be called to order (or if any of these circumstances arises after the meeting has been called to order, it will be adjourned or suspended until quorum is reestablished) and will be rescheduled. The IRB staff will monitor the members that are present at the meeting and determine that the meetings are appropriately convened and remain so.

In order for the research to be approved at the convened meeting it must receive the approval of a majority of the members present at the meeting. The IRB roster will show which members are in attendance for each vote taken during an IRB meeting.

Votes submitted prior to a convened meeting by mail, telephone, fax or e-mail are not permissible. Comments of the absent members may be submitted and considered by the attending IRB members.

### **6.8 IRB Records**

#### **IRB Membership Roster**

The IRB maintains rosters of IRB membership including: name, earned degrees, representative capacity, experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the Institution. Changes to the IRB membership roster are reported to OHRP by the IRB Staff or IRB Director.

## Written Procedures and Guidelines

The IRB maintains written procedures as required by [45 CFR 46.103\(b\)\(4\), \(5\)](#).

## Meeting Minutes

For each IRB, an IRB administrator will maintain detailed records of meeting minutes that will specify which members were present, that a quorum was maintained for each action, the number of votes for each action during the meeting, documentation of a non-scientist member for each vote, and documentation that an IRB member knowledgeable about or experienced in working with specific/vulnerable populations was assigned as a reviewer and/or was present for the vote.

Each IRB will keep a roster of all members and, for each action, record which members voted. This document will be kept separate from the distributed minutes.

Additionally, IRB staff shall document all meeting minutes according to federal regulations and the requirements listed below.

The IRB meeting minutes include:

- Confirmation that quorum was maintained for each vote
- Attendance for each action
- Summary of discussion of controversial issues (if any) and their resolution
- Record of IRB decisions (actions taken by the IRB)
- Record of voting (including the number of members voting for, against, and abstaining) for each action
- The basis for requiring changes in or disapproving research
- Names of IRB member(s) recused and not present during the discussion or vote in any research protocol under review and of those who abstain due to conflicts of interest
- Description of the materials reviewed for both new and continuing review proposals. Such materials might include the IRB application, clinical protocol, investigators brochure, informed consent form documents, continuing review form, primary reviewer's evaluation (for continuing review) and any other materials submitted for review



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- All applicable waivers are discussed and documented (with justification) in the IRB minutes including, waiver or alteration of informed consent and written informed consent
- Protocol specific determinations on studies involving vulnerable populations (45CFR46 Subparts B, C, D) are documented and justified according to the regulations
- Approval period for initial and continuing reviews
- Rationale for significant risk/non-significant risk device determinations
- If an IRB member has a Conflict of Interest regarding a study being reviewed, they will recuse themselves from the review of the study. The name and reason for absence will be included in the minutes
- When an alternate member replaced a primary member

Minutes from each IRB meeting are distributed to all IRB members, to the Vice President of Research and relevant institutional administration for review according to the Federalwide Assurance. IRB members are required to review the minutes and note any corrections or additions at the first meeting following distribution of the minutes.

### **Records Retained in the IRB Files**

IRB files contain the following documents and information for each study:

- iStar application
- Draft/Approved consent documents
- Clinical protocol, including amendments/revisions
- Investigators brochure(s)
- Grant application(s)
- Scientific evaluations, if any, that accompany the proposals
- Budget
- Supporting information that accompanies the studies (staff reviews, recruitment documents, IRB reviews)

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- Amendments
- Reportable events
- Category of approval for exempt, expedited, Full Board (when necessary), and continuing review submissions
- Progress reports submitted by investigators
- All continuing review activities
- Reports of injuries to subjects
- Statements of significant new information/findings provided to subjects
- Emergency use reports
- IRB minutes
- Correspondence between the IRBs and investigator

### Record Retention Requirements

Copies of all documentation relating to IRB review, even when a project is cancelled without subject enrollment, are maintained by the IRB office. Generally, records are maintained for a minimum of three years after completion of the research or as determined by the University's policy or sponsor requirements. Additionally, in accordance with federal HIPAA privacy regulations, records containing protected health information are retained for at least six years after completion of the research. However, USC, like many research institutions, retains IRB research records indefinitely.

For additional information, refer to the [USC Record Retention Policy](#).

### Access to Files

IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

## **6.9 Development, Approval, and Maintenance of IRB Policies and Procedures**

The USC IRB Policies and Procedures are written and applied according to federal regulations and state and local laws. In addition, University policies and procedures, and accrediting and funding agencies policies will be considered. To assure continued compliance, the following will be conducted:

- USC IRB policies and procedures are to be reviewed every three years and when changes in regulations, laws, and institutional policies necessitate revision
- USC IRB policies and procedures are developed and maintained by the Human Subjects Working Group under the direction of the Executive Director for the Office of the Protection for Research Subjects
- The HSPP is charged with the appropriate implementation and enforcement of IRB policies and procedures consistent with other University policies and procedures

### **Investigator Responsibilities with Respect to Policies**

The investigator will review USC IRB policies and procedures as part of the required initial training for conducting human subjects' research at the University of Southern California. Current policies and procedures are located on the IRB website at <http://oprs.usc.edu/rules/>. It is the responsibility of the investigator to routinely view the IRB website for new or revised IRB policies and procedures. The investigator should contact IRB staff for clarification of policies and procedures, when necessary.

### **IRB Staff Responsibilities with Respect to Policies**

IRB staff will routinely view the OHRP and FDA websites for issuance of guidance documents, changes in regulations, and determination letters. The IRB Working Group will contact the Office of General Counsel and Office of Compliance, when necessary, to discuss changes and assist in the interpretation of federal, state and local regulations affecting IRB policies and procedures. The IRB staff and Office for the Protection of Research Subjects staff will provide educational sessions to the IRB members and staff regarding IRB policies and procedures, as well as updates or revisions.

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The IRB staff will use the IRB policies and procedures posted on the IRB website when reviewing IRB applications. The IRB staff may consult with other IRB officials for guidance in applying the IRB policies and procedures. If the IRB staff notices that a policy or procedure is inaccurate or out of date, he/she should bring it to the attention of the IRB Director who will communicate to the Human Subjects Working Group. It is the responsibility of all IRB staff to assist in keeping the IRB policies and procedures current and applicable to the daily processes of the IRB offices and to follow the policies as stated.

## Chapter 7: Types of IRB Submissions

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# Chapter 7

## Types of IRB Submissions

All USC human subjects research projects must undergo review and approval by an IRB prior to initiating research activities. This chapter defines human subjects research, outlines what kind of studies require and do not require IRB approval and details the types of submissions and review categories.

This chapter will establish what Human Subjects Research is and what is not Human Subjects Research followed by an overview of types of IRB submissions.

The USC IRBs review all human subjects research activities at USC to determine the appropriate category of review. An investigator may request a particular category of IRB review however; the final determination is made by the IRB.

### JIT (Just-in-Time) Submission

Just-in-Time IRB review may be requested for NIH funded studies with a likelihood of being funded. When IRB approval is requested via the Just-in-Time process – the time sensitive request will be given IRB review priority. The investigator must indicate in the iStar submission that a Just-in-Time review is being requested and provide the NIH verification of this request.

## 7.1 Human Subjects Research: What is and What is Not

The initial determination of whether a study is or is not human subjects research is made by referring to the federal ([45 CFR 46](#)) definitions of human subjects and research (FDA has slightly different definitions). Any activity that meets OHRP definitions of both “research” and “human subjects” or the FDA definitions of both “clinical investigation” and “human subjects” is considered human subjects research.

### What is Human Subjects Research (HSR)

#### Defining Human Subjects

**OHRP** (45 part 46) defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, information which has been provided for specific purposes by an individual and the individual reasonably expects the information will not be made public (for example, a medical record). Private information must be individually identifiable (the identity of the subject is already associated with the information, or may readily be ascertained by the investigator) in order for obtaining the information to constitute research involving human subjects.

**FDA** (21 part 50.3) defines a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.”

When an investigational device is used on a specimen, the specimen may be considered a “human subject” under FDA definitions.

Note: The **Department of Defense (DOD)** [32 CFR 219.102(f) reference (c)] defines “Research Involving a Human Being as an Experimental Subject” as: “An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the

withholding of an intervention that would have been undertaken if not for the research purpose.” (DODD 3216.02, E2.1.3)

### Defining Research

**OHRP** (45 part 46) defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.

**FDA** (21 part 50.3) defines “clinical investigation” as “any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies.”

Note: Sections 505(i) and 520(g) refer to any use of a drug other than the use of an approved drug in the course of medical practice and 520(g) refers to any use of a medical device other than the use of an approved medical device in the course of medical practice.

### What is Not Human Subjects Research (NHSR)

Certain activities have the characteristics of research but do not meet the federal definition of research and/or the federal definition of human subjects according to OHRP and FDA regulations. Examples of NHSR are classroom research, institutional research, oral history, research with autopsy specimens, program evaluations, quality improvement projects and literature searches.

If it is clear after reading the preceding examples, that the research study does NOT require approval by the IRB, it does NOT need to be submitted to the IRB. If there is a question as to whether the study requires approval by the IRB, contact the IRB office. If a study does not meet the definition of human subjects or research, the IRB can issue a letter, if requested by the investigator, stating that the study does not qualify as human subjects research and therefore does not need to be approved by the IRB. Refer to [Section 7.5 – Not Human Subjects Research \(NHSR\) Submissions](#).



**OHRP** (45 Part 46) defines a human subject as a "living" individual, so research involving autopsy materials or cadavers is not considered human subjects research and does not require review by the IRB. The activity may still be subject to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Contact the IRB office for questions.

The intent to publish in professional journals and/or present at national or regional meetings does not automatically make a project human subjects research requiring IRB review and approval. If you have questions regarding publishing or presenting, please contact the IRB office for further guidance.

Now that HSR and NHR have been established, the various submission types will be discussed.

### 7.2 Exempt Review

Research activities in which the only involvement of human subjects will be in one or more of the categories listed below are exempt from federal regulations listed under 45 CFR 46.101, unless otherwise required by department or agency heads [[45 CFR 46.101\(b\)](#)]. Exempt review studies require IRB submission. The IRB determines whether a study qualifies as an exempt study; investigators do not have the authority to make exempt determination themselves. Informed Consent documents are not required and will not be reviewed by the IRB. (The application provides a link to the consent template forms if researchers still choose to use them.) Recruitment material will not be reviewed for exempt studies. (See also 8.3 [Review of Exempt Research](#))

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
  - i. Research on regular and special education instructional strategies, or
  - ii. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

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- i. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects;
  - ii. and any disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 45 CFR 46.101(b)(2) if:
  - i. The human subjects are elected or appointed public officials or candidates for public office; or
  - ii. Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
  - i. Public benefit or service programs
  - ii. Procedures for obtaining benefits or services under those programs
  - iii. Possible changes in, or alternatives to, those programs or procedures, or
  - iv. Possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies,
  - i. if wholesome foods without additives are consumed

- ii. or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe or agricultural chemical or environmental contaminant at or below the level found to be safe by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

### General Restrictions on Exempt Review

For research involving prisoners, exemption categories DO NOT apply [[45 CFR 46.101\(i\)](#)].

For research involving children, exemption category 2 DOES NOT apply unless research only involves observation of public behavior when the investigator(s) do not participate in the activities being observed.

FDA does not recognize exemption categories 1 through 5. Only exempt category 6 may qualify as exempt.

Deception in exempt research is discussed in [Section 17.9 – Research Using Deception](#).

### Duration of Project Approval

Exempt studies do not expire and do not require annual IRB review of the project. However, if changes to the study are proposed that may affect the risk/benefit ratio of the study, investigators must inform the IRB. Additionally, when a study is completed or terminated, investigators should update the status of the IRB application (refer to [Section 9.3 – Project Closure](#)).

## 7.3 Expedited Review

The IRB may use an expedited procedure to conduct initial review of research provided that research activities do not fall under any of the general restrictions, present no more than minimal risk to human subjects, and involve procedures listed in one or more of the following categories (45 CFR 46.110(a)/21 CFR 56.110(a)):

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

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- a. Research on drugs for which an investigational new drug application 21 CFR Part 312 is not required. (NOTE: Research on marketed drugs that significantly increases the risks, or decreases the acceptability of the risks associated with the use of the product, is not eligible for expedited review.)
  - b. Research on medical devices for which:
    - i. an investigational device exemption application [21 CFR Part 812](#) is not required, or
    - ii. the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
- a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week, or
  - b. From other adults and children\*, when the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected are considered. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period and collection may not occur more frequently than two times per week.
- \*Children are defined in the federal regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" see [45 CFR 46.402\(a\)](#).
3. Prospective collection of biological specimens for research purposes by noninvasive means.

## Chapter 7: Types of IRB Submissions

Examples: (a) Hair and nail clippings in a non-disfiguring manner; (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) Permanent teeth if routine patient care indicates a need for extraction; (d) Excreta and external secretions (including sweat); (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) Placenta removed at delivery; (g) Amniotic fluid obtained at the time of rupture of the membrane before or during labor (h) Supra and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) Mucosal and skin cells collected by buccal scrapping or swab, skin swab, or mouth washings; (j) Sputum collected after saline mist nebulization; (k) Vaginal swabs that do not go beyond the cervical os; (l) Rectal swabs that do not go beyond the rectum; and/or (m) Nasal swabs that do not go beyond the nares (procedures k-m addressed on [OHRP Correspondence 9/22/11](#), “Clarification of ‘noninvasive’ in expedited review category 3”).

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.

Examples: (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) Weighing or testing sensory acuity; (c) Magnetic resonance imaging; (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may meet exemption under [45 CFR 46.101\(b\) \(4\)](#). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may meet exemption under [45 CFR 46.101\(b\) \(2\)](#); this listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by a full IRB as follows:
  - a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - b. Where no subjects have ever been enrolled and no additional risks have been identified; or
  - c. Where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened full IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified.

### General Restrictions on Expedited Review

- Expedited review procedures may not be used for research involving prisoners unless the research is minimal risk and meets the criteria of expedited review as indicated in the federal regulations ([45 CFR 46, Subpart C](#)). In most cases, expedited review procedures are not appropriate for research involving prisoners. However, if a project meets the criteria for expedited review, the IRB Chair/Vice Chair or designee will consult with the prisoner representative of the IRB to determine if the submission could be reviewed by expedited procedures. If the prisoner representative agrees that expedited procedures are appropriate, the representative will be assigned as one of the designated reviewers. For more information on prisoner research, refer to [Section 14.3 – Prisoners in Research](#).
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review process may not be used in the review of classified research (such as DOD projects).

### Duration of Project Approval for FDA Regulated Studies

FDA regulations require that every approved study receive continuing review “not less than once per year.” Accordingly, an approval period of an FDA regulated study cannot exceed 364 days.

Each IRB approval letter notes an initial approval date and an expiration date. The initial approval date is the date all contingencies are satisfied.

<http://www.hhs.gov/ohrp/policy/continuingreview2010.html#section-g2> and <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>.

### 7.4 Full Board Review

All human subjects research projects involving more than minimal risks to subjects (or involving minimal risk to subjects but do not qualify for expedited review) are reviewed at a fully-convened IRB meeting. A majority of IRB members must be present to conduct the meeting and to satisfy voting requirements. At least one member whose primary concern is in nonscientific areas and at least one member who is not affiliated with USC must be present.

#### Duration of Project Approval

Federal regulations adhered to by USC require that every approved study receive continuing review “not less than once per year.” Accordingly, an approval period cannot exceed 364 days. In some cases, the IRB may grant a shorter approval period if the complexity or risk level merits more frequent continuing review. Examples include: the nature of risks posed by the study, the degree of uncertainty regarding the risks involved, the vulnerability of the subject population, the experience of the clinical investigator in conducting clinical research, the IRB’s previous experience with the investigator and/or sponsor, the projected rate of involvement and whether the study involves novel therapies. Alternatively, the IRB may grant an approval period based on a number of subjects accrued, rather than a specific time period. This type of approval period is usually assigned when there are questions regarding the potential risks of participation.

Each IRB approval letter notes an initial approval date and an ending approval date. The initial approval date is the date all contingencies are satisfied. The procedure for setting the effective approval date and the duration of protocol approval are based on harmonized guidance from the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA). For additional information, refer to <http://www.hhs.gov/ohrp/policy/continuingreview2010.html#section-g2> and <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>.

### 7.5 Not Human Subjects Research (NHSR) Submissions

A Not Human Subjects Research (NHSR) submission is an information request to determine if a project is subject to IRB review and approval. Its purpose is to streamline



the system to exclude projects that do not meet the regulatory definitions of human subjects research. If a project submitted as NHSR is determined to be a human subjects research study, a new study application will be requested by the IRB.

Studies are considered “Not Research” when they do not meet the [45 CFR 46](#) definitions of human subjects and/or research. Investigators who believe their project may qualify as NHSR can submit an on-line request “Does my project qualify as Not Human Subjects Research?” through the iStar system. This determination is made by the IRB / IRB designee and not by the investigator.

Projects that involve FDA-regulated products are required to be submitted as an IRB application. If a project involving FDA-regulated products is submitted through the NHSR information request it will be returned with instructions to submit a regular IRB application.

### 7.6 Coded Specimens / Data Submissions

The Office for Human Research Protections (OHRP) considers private information, or specimens, not to be identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Study of specimens or data that meet this criterion is considered as not human subject research. ([Guidance on Research Involving Coded Private Information or Biological Specimens](#)). This type of study submission is applicable when both of the following conditions are met:

- 1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with individuals; and
- 2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
  - (a) The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the

HHS regulations do not require the IRB to review and approve this agreement); or

- (b) There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
- (c) There are other legal requirements prohibiting the release of the key to the investigators.

### 7.7 Newborn Dried Bloodspots

The Newborn Screening Saves Lives Reauthorization Act of 2014 explicitly states that the use of newborn dried bloodspots for research is considered to involve human subjects if the research is federally supported and the bloodspots are collected on or after March 18, 2015. The identifiability (or not) of the bloodspots is irrelevant. In other words, if a researcher is receiving de-identified or anonymous bloodspots for research, the research is considered to involve human subjects. A detailed summary of recommendations is provided by the U.S. Department of Health and Human Services, Secretary's Advisory Committee on Human Research Protection (SACHRP). The goal of this recommendation is to provide thoughtful consideration of this act and allow for important research to take place. Refer to: <https://oprs.usc.edu/files/2016/05/SACHRP-Newborn-Dried-Bloodspots.docx>

### 7.8 Just-in-Time (JIT) Submission

Just-in-Time IRB review may be requested for NIH funded studies with a likelihood of being funded. When IRB approval is requested via the Just-in-Time process – the time sensitive request will be given IRB review priority. The investigator must indicate in the iStar submission that a Just-in-Time review is being requested and provide the NIH verification of this request.

### 7.9 Grant and Contract Only Submissions

Grant and Contract Only submissions are projects that lack definite plans for involvement of human subjects. When necessary to satisfy a funding sponsor, the Principal Investigator (PI) may submit a grant/contract application through iStar. The PI must submit a new study application and receive IRB approval prior study initiation or any human subject involvement.

Grant and Contract Only Submissions include:

- Applications for approval of Center, Training or Program Project Grants, where the application outlines the administrative core requirements and does not include a plan for the involvement of human subjects. Review of data coordinating centers, or similar entities that involve access to private and identifiable information about living individuals, requires review by a designated or expedited reviewer.
- Applications requesting approval for development purposes only under [45 CFR 46.118](#) and [46.119](#), where the proposals lack definite plans for the inclusion of human subjects.

The IRB will review an application and send correspondence acknowledging the submission of the grant and that the project does not have definite plans to involve human subjects. Except for research waived under 46.101(i) or 46.104, no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB and certification submitted, by the institution, to the Federal department or agency component supporting the research.

The IRB will require acknowledgment from the PI that regulation requirements will be met.

### 7.10 Humanitarian Use Device

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the

development of devices for use in the treatment or diagnosis of diseases affecting these populations.

An approved Humanitarian Device Exemption (HDE) application authorizes marketing of the HUD.

Use of an HUD for its approved indication does not constitute human subjects research. However, FDA regulations require that the Institution's IRB review and approve the use of the HUD at the Institution. The IRB's responsibility in this case is to conduct a special limited review to verify that the proposed (non-research) use of the device is consistent with the HDE's FDA-approved indication (21 CFR 814.124(a)). After granting initial approval, the IRB may use expedited procedures for conducting subsequent continuing reviews, which must be performed at least annually. FDA regulations do not require an informed consent form for clinical use of an HUD. However, sponsors often provide a sample consent form and the IRB or the Institution may require the investigator to use an informed consent form specific for HUDs. For additional information, refer to [Section 18.5 - Humanitarian Use Devices \(HUD\)](#).

### 7.11 International Research

USC faculty or students who intend to conduct human subjects research abroad must obtain USC IRB approval prior to commencing research activities. Research conducted outside the U.S. must respect applicable national laws as well as U.S. regulatory expectations.

If a study involves more than minimal risk, investigators will be required to obtain approval from a Research Ethics Board, IRB equivalent, or a ministry of health from within the country where the research is being conducted. Local collaborators and local IRBs can provide insight on local laws, such as those pertaining to privacy. Research may be restricted in certain countries based on different privacy and/or data security rules, or rules pertaining to the export of personally identifiable data. As determined by the IRB, an expert in the culture of the other country may be used in lieu of the IRB equivalent.

USC IRB has no oversight responsibility when research with human subjects is performed at another site by USC faculty members who are on an unpaid leave of absence, or are otherwise not conducting research in connection with their USC responsibilities. If the faculty member brings back identifiable private or intends to continue the research at USC, a new USC IRB application must be submitted.

## Chapter 7: Types of IRB Submissions

Many international universities have Ethics Committees that can review and approve research. HHS provides a resource to identify federally assured sites that is updated annually: <http://www.hhs.gov/ohrp/international/index.html>

If a study involves minimal risk, the IRB equivalent to an approval letter or permission letter from the research site may be acceptable. The USC IRB will review these on a case-by-case basis. Investigators are encouraged to contact the Chair of the appropriate USC IRB to discuss issues related to International Research.

All international research studies must adhere to recognized Ethics Codes such as [Title 45 CFR 46](#), the [Declaration of Helsinki](#), the [Nuremberg Code](#), or the [Belmont Report](#). Consent and recruitment documents must be in the language that is readable and understandable by the subjects or the short form and translator method may be used.

International research must also conform to USC's policy on International Collaborations and Export Controls, as applicable: <http://research.usc.edu/international-research/>

### *Helpful Links*

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- [Ethics of International Research](#) (USC)
- [Resources for International Research](#) (OHRP)
- [Compilation of International Human Research Standards pdf](#)
- [Good Clinical Practice](#) (International Conference on Harmonization)
- [International Ethical Guidelines for Biomedical Research Involving Human Subjects](#) (CIOMS)
- [Following the Guideline of the International Conference on Harmonization – Good Clinical Practice \(E6\)](#) (AAHRPP)
- [The Eubios Ethics Institute](#) (Japan)
- [Canadian Institutes of Health Research](#)
- [National Council on Ethics in Human Research](#) (Canada)

### 7.12 Continuing Review

In accordance with federal regulations, the USC IRB requires that ongoing research protocols undergo continuing review at intervals appropriate to the degree of risk, but not less than once per year. The frequency and extent of continuing review for each study is based upon the nature of the study, the degree of risk involved, the novelty of the research procedures, the experience of the clinical investigator in conducting clinical research, the IRB's previous experience with the investigator and/or sponsor, the projected rate of enrollment and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be re-reviewed by the IRB. In some instances, such as when research involves the use of innovative techniques, the IRB may choose to grant an approval period based on a small number of subjects accrued rather than on a specific time period. This type of approval is usually assigned when there are concerns regarding the potential risks of participation.

Each investigator must abide by the approval period imposed by the IRB at the time of the most recent IRB approval. Each IRB approval notice designates a period of time during which activities involving human research subjects may be undertaken. No research project may continue to recruit, enroll, or treat subjects or analyze data after the IRB approval expiration date. Continuation of the research after the date of expiration of IRB approval is a violation of federal regulations.

To assist investigators in fulfilling the requirement for continuing review, the IRB sends expiration notices through iStar at 90, 60, 45, and 30 days prior to expiration to the investigator, faculty advisor, and study coordinator. If investigators do not submit a completed application for continuing review at least 30 days before the protocol expiration date, the IRB cannot guarantee that the application will be reviewed before the date of expiration.

It is the investigator's responsibility to ensure that approval for an active protocol remains current. The IRB expiration date can be found on the main study page in the iStar online submission system, in the IRB approval letter, and in the expiration notices.

For more information, refer to [Section 9.2 – Continuing Review](#).

Note: Studies involving less than minimal risk and that are not federally funded can be reviewed at intervals greater than once per year under the [USC Flexibility policy](#).

### 7.13 Amendments – Changes to Research after Approval

The IRB requires investigators to submit modifications to previously approved studies through an amendment in iStar. IRB approval of the amendment must be granted before any changes in research activity are made. When a change is necessary to eliminate apparent immediate hazards to the research subjects or others, the investigator must promptly (within 30 days) inform the IRB of the change by submitting a reportable event in iStar. The IRB will review the change to determine that it was consistent with ensuring participants' continued welfare. The IRB approval letter sent to the investigator outlines this responsibility.

#### Significant New Information / Findings

Significant New Information/Findings relating to protocol changes should be provided to participants when such information might relate to their willingness to continue to take part in the research. Significant New Information/Findings, can be provided to subjects in various ways depending on urgency (refer to [Section 10.15 – Providing Significant New Information and/or Findings \(SNIF\) to Participants](#) for more information).

Investigators should be aware that certain modifications may require changes in the budget or contract agreements with the sponsor or funding agency. Investigators should contact the Clinical Trials Office and/or the Department of Contracts and Grants to discuss the need for budget or contract changes.

Investigators should also be aware that the original expiration date of a study does not change when an amendment is approved by the IRB. Expiration dates change only at the time of continuing review.

### 7.14 Reportable Events

USC investigators are required to inform the IRB about specific events that occur in a study. These are called reportable events. An overview of reportable events including definitions and reporting timeline is provided here. For detailed information about reportable events, refer to [Section 9.8 – Reportable Events](#) and [Chapter 20 – Reportable Events, Noncompliance, Suspensions, and Terminations](#).

### Adverse Events

Adverse events (AEs) are defined as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” by the Federal Drug Administration (FDA). In contrast, the Office for Human Research Protections, (OHRP), defines adverse events as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.”

At USC, only AEs that are unexpected, related or possibly related, and are either serious or place subjects or others at a greater risk of harm than was previously known or recognized, must be reported to the IRB through iStar, using the Reportable Event application. Reporting to the USC IRB must be as soon as possible, but not later than 10 working days after the investigator becomes aware of the event.

Additional requirements are in effect for investigators who are also sponsors (sponsor-investigators). Refer to [Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators](#) and [Section 18.4 – Sponsor-Investigators](#) for additional information.

### Adverse Device Effects

An unanticipated adverse device effect (UADE) is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects”.

UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. Investigators must report the UADE to the IRB through the Reportable Event application in the iStar system.

Additional requirements are in effect for investigators who are also sponsors (sponsor-investigators). Refer to [Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators](#) and [Section 18.4 – Sponsor-Investigators](#) for additional information.



### Unanticipated Problems Involving Risk to Subjects or Others (UPX)

An unanticipated problem involving risks to subjects or others (UPX) includes any incident, experience, or outcome that meets all of the following criteria:

- ***unexpected*** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- ***related or possibly related*** to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and
- suggests that the research ***places subjects or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) ***than was previously known or recognized***

UPXs should be reported to the IRB as soon as possible, but not later than 10 working days after the investigator becomes aware of the event, using the Reportable Event application in iStar. For sponsored research, the terms of the contract may define a shorter reporting timeframe.

PIs of research reviewed and approved by the NCI CIRB are responsible for reporting any potential UPXs occurring at the local site. The PI submits a reportable event application in iStar. If the event is determined to be a UPX, the PI must report the event to the NCI CIRB.

### Noncompliance in Research

Noncompliance is the failure to follow federal, state, local, or institutional regulations and policies governing human research or failure to comply with the determinations of the IRB. Noncompliance may involve any individual conducting research.

Additionally, if any reasonable individual would foresee the event as compromising the rights and welfare of a subject or others, the noncompliance may be considered **serious**.

If the noncompliance recurs after a report of the activity has been evaluated and

corrective action has been mandated, noncompliance may be deemed to be **continuing** noncompliance.

### Protocol Deviations

A protocol deviation refers to those occasions when protocol required procedures are accidentally or intentionally not met. The determination as to which deviations or errors must be reported to the IRB is driven by sponsor/monitor requests or concerns of the principal investigator or study staff, it is not defined by regulation. When the determination is made to report a deviation, it should be submitted through iStar as a reportable event.

### Participant Complaints

A participant complaint is an expression of dissatisfaction by the participant (or his/her representative) that may or may not involve a breach in human subjects rights or research ethics. Participants may choose to report complaints to the study team, the IRB, or to a third party (such as hospital administration). Therefore, it is important that during the consent process, subjects receive consent forms and information sheets that include investigator and IRB contact information so that participants have resources to ask questions about the study and report complaints.

Subject complaints must be reported using “Participant Complaint” form in the iStar “Reportable Events” application for IRB review and resolution.

## 7.15 Clinical Trial Progress Reports

In addition to routine, continuing review by the IRB, some clinical trials must submit periodic reports to the IRB, particularly those related to safety progress reports including data safety monitoring reports and annual reports for Investigational Device Exemption studies.

### Data Safety Monitoring Reports

A data safety monitoring report is an interim analysis in a clinical trial, conducted by a committee independent of the research team and the IRB, such as a Data Safety

Monitoring Board or a Data Monitoring Committee. The report is submitted to the IRB through the iStar reportable event application. For additional information about Data Safety Monitoring, refer to [Section 21.2 – Data Safety Monitoring Board](#).

### **Investigational Device Exemption (IDE) Annual Report**

Investigators conducting research with a device subject to Investigational Device Exemption (IDE) regulations must submit annual progress reports to the IRB. The annual IDE report is submitted to the IRB through the iStar reportable event application.

Investigators who are also sponsors of an IDE study must comply with additional regulations (refer to [Section 18.4 – Sponsor-Investigators](#)). For additional information about Investigational Device Exemptions, refer to [Section 18.3 – Investigational Medical Devices](#).

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## **Chapter 8**

# **Process of IRB Submissions**

This chapter focuses on the IRB submission and review processes. It includes an overview of iStar, the electronic application system used to submit all human subjects proposals to the IRB, the criteria for IRB approval, the review process for the different submission types, and IRB determinations and correspondence details.

### **8.1 IRB Online Application (iStar)**

The IRB Submission Tracking and Review (iStar) online system supports all applications: new study, continuing review, amendment, and reportable event (for safety and other reports). Access to the iStar system is granted to the research team and IRB staff depending on roles and oversight responsibilities.

The application guides users to questions specific to the nature of their research, and ensures that information required for regulatory purposes is appropriately collected. For example, if a protocol includes minor subjects, users are required to select a child risk category and explain the process for obtaining assent and parental permission.

iStar maintains the currently approved study. With each amendment submission, the investigator is required to update the previously approved study to reflect the changes under review. iStar systematically records all changes and stores previous versions of the application and study documents in an accessible manner.

Among the documents available in iStar are:

- iStar submission (initial and continuing review)
- Informed consent and assent forms (if applicable, these documents are available in both approved and draft form)
- Scientific protocol
- Study grant
- Recruitment documents

- Surveys and questionnaires
- Approval documents from collaborating Institutions
- Ancillary committee approvals
- Reportable events and reports
- IRB and study team correspondence
- IRB approval notices
- Other documents related to IRB review

In addition to being a submission and document storage system, iStar creates historical records and provides audit trails of the IRB review process. All study-specific correspondence between the research team and the IRB are created and stored in iStar.

### 8.2 ClinicalTrials.gov

ClinicalTrials.gov is a database of both publicly and privately supported clinical studies that are conducted for participants around the world, located at the National Library of Medicine.

On September 16th, 2016, The U.S. Department of Health and Human Services expanded requirements for registration and results information to [clinicaltrials.gov](https://clinicaltrials.gov) for FDA-regulated drug, biological, and device products. Simultaneously, NIH issued a policy requiring registration and results information to [clinicaltrials.gov](https://clinicaltrials.gov) for all NIH-sponsored clinical trials, regardless of whether the trial is covered by the HHS Final Rule.

Registration and results reporting are required for applicable clinical trials; however, [ClinicalTrials.gov](https://clinicaltrials.gov) allows voluntary reporting of other studies that:

- Are in conformance with any applicable human subject or ethics review regulations (or equivalent) and
- Are in conformance with any applicable regulations of the national (or regional) health authority (or equivalent) Investigators may choose to register a study that is not an applicable clinical trial as a condition to publish study results in a journal. FDA regulations require reporting of results from registered trials.

## Chapter 8: Process of IRB Submissions

The Responsible Party must generally report results no later than 12 months after the trial completion date. Results must include participant baseline characteristics, participant flow diagram, outcomes, and adverse events. Instructions for submitting results are available at [ClinicalTrials.gov](https://clinicaltrials.gov). FDA also requires sponsors or investigators to certify compliance with [ClinicalTrials.gov](https://clinicaltrials.gov) registration when submitting certain applications to the FDA. Form FDA 3674 is used to certify compliance.”

**The text above may be used in NIH applications requiring a statement of USC policy.**

Registration is required by [law](#) per [Section 801 of the Food and Drug Administration Amendments Act](#) and the [Final Rule for Clinical Trials Registration and Results Information Submission \(September 2016\)](#) for:

- [FDA Clinical Trials](#) defined as intervention studies that include drugs, biological products, and medical devices;
- [NIH Clinical Trials](#) defined as biomedical and behavioral studies of human subjects;
- Publication of research studies that assigns human subjects to health-related interventions and evaluates their outcomes. Other public registries are also available to meet criteria for [ICMJE](#) and [WHO](#); and
  - Reimbursement of [Medicare](#) claims for items and services in clinical trials that are qualified for coverage.

Registration of an applicable clinical trial must be submitted no later than **21 days** after enrollment of the first participant.

**Non-compliance of these requirements may result in civil monetary penalties, withholding/recovery of federal funds, and/or withholding of publications.**

Principal Investigators are responsible to register their studies prior to participant enrollment in the [Protocol Registration System \(PRS\)](#) of [ClinicalTrials.gov](https://clinicaltrials.gov).

For additional information refer to [USC Guidance for Registering at ClinicalTrials.gov](#) .

### 8.3 Criteria for IRB Approval of Research

In order to approve research, federal regulations ([45 CFR 46.111](#)) require that the IRB (reviewer or Full Board) determine that all of the following requirements are satisfied:

## Chapter 8: Process of IRB Submissions

- Risks to subjects are minimized: (a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the IRB must take into account the purpose(s) of the research and the setting in which the research will be conducted and must be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by [45 CFR 46.116](#).
- Informed consent will be appropriately documented, in accordance with, and to the extent required by [45 CFR 46.117](#).
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, the IRB will ensure additional safeguards have been included in the study to protect the rights and welfare of these subjects. Refer to [Chapter 14 – Vulnerable Subject Populations](#).



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In addition to these regulations, the IRB must also consider:

- PI/study team qualifications, including credentialing and hospital privileges
- Adequacy of research description and methodology
- Certification that all study personnel have completed required training
- Conflict of Interest (PI and study staff)
- Subject recruitment
- Privacy and confidentiality
- Risk/benefit ratio
- HIPAA applicability and waivers
- [Scientific merit](#)
- [Budget review](#)
- California laws and university policies

The IRB evaluates the responses provided in all corresponding subject sections of the iStar submission application to determine that the study will be conducted in accordance with applicable regulations and requirements.

### Review of Scientific Merit

Scientific merit is a basic expectation of human subject research and is an integral part of the IRB review. It is not ethical to expose subjects to risk and inconvenience if the research has no merit. Review of biomedical studies will take into consideration any scientific review conducted by other committees or outside entities before the study was submitted to the IRB.

Non-cancer, investigator-initiated clinical trials that had no prior scientific review are forwarded to the SC-CTSI for scientific review committee for evaluation. The review process is integrated into the iStar application and the IRB process will continue once the committee review is complete.

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Federal regulations ([45 CFR 46](#)) as well as the Association for the Accreditation of Human Research Protection Programs ([AAHRPP](#)) require the IRB to review the scientific merit of proposals.

Peer or scientific review by USC institutional scientific committees such as the Cancer Center Clinical Investigations Committee and the Clinical Trials Unit (CTU), reviews by committees external to USC such as NIH cooperative groups, NIH study sections, sponsor review committee(s), and regulatory agencies such as the Food and Drug Administration provide assurance that experts have evaluated the study and found it meritorious. When protocols have not undergone peer/scientific review, additional reviewers with knowledge in the relevant discipline may be assigned to provide confidence in the scientific merit of the study. This process assures that in addition to all other review criteria scientific merit is properly addressed.

The IRB reviews all studies to ensure that:

- The research uses procedures consistent with sound research design
- The research design could allow the proposed research questions to be answered
- The risk/benefit relationship is acceptable
- The purpose and specific aims are clear and feasible, and the research will contribute to generalizable knowledge

Experts agree that the IRB should approve only research that is both valid (can answer questions posed) and of value. The IRB may request for an expert consultant to review a proposed research project or defer to scientific review committees in order to determine whether a study has sufficient scientific value (merit) and/or if a study design places subjects at unnecessary risk. Before the consultant reviews the study, the IRB office will confirm with the consultant(s) that there is no potential conflict of interest.

**Student research** is expected to be reviewed by a dissertation committee for scientific validity. Further, projects that do not provide an actual benefit to society or have compelling scientific merit can still be approved by the IRB if all other approval criteria are met.

For **Department of Defense** sponsored research, review of scientific merit is required prior to initial IRB approval. In addition, any substantive amendment to approved

research sponsored by DOD must undergo scientific review prior to the review by the convened IRB.

### Review of Research Funds/Budget

Assurance of adequate financial resources for proposed research is inherent in the IRB's responsibilities and obligations in the protection of human subjects. Subjects may be put at risk if the protocol cannot be carried out as approved, due to inadequate resources. In most cases the IRB will rely on access to budget information through the Kuali Coeus system for review. When a biomedical study is not funded by an external sponsor, the department/school representative must attest that all study costs are guaranteed. The department chair has the option of assigning budget approval to either the division level or department level representative.

The IRB will not approve a study when requests for documentation of funding information are not satisfied. For social behavioral studies, no department approval is required, except in exceptional cases, and in the Ostrow School and Pharmacy School, where single level approval is required.

Also see [USC Conflict of Interest Policies](#)

## 8.4 Review of Exempt Research

To obtain an exempt determination, the investigator must submit an exempt iStar application.

At USC, designated staff and IRB members have the authority to approve exempt studies. Reviewers of exempt determinations conduct a review of the project to determine if it qualifies for exempt status according to IRB policy, human subjects research regulations, and ethical standards. To facilitate review, additional revisions may be requested by the IRB. If the study does qualify, the PI is notified, and no further IRB review is needed.

When the study does not meet exempt criteria, the IRB staff and/or designee determines the appropriate level of review, notifies the investigator, and guides the investigator with resubmission at the required level. If exempt determination is unclear, the Chair, Vice Chair, or designee may assist with the determination. Exempt determinations are distributed to all IRB members electronically and acknowledged by each committee.

IRB reviewers have access to all necessary application materials in the iStar system, including:

- A completed [iStar](#) application with conflict of interest statement
- Proposed information sheet(s) and/or scripts as appropriate
- Surveys, questionnaires, or videos
- Relevant grant applications

### Amendments and Revisions to Exempt Research

Once a project is determined by the IRB to be exempt, changes (such as personnel, methodology/procedures, subject population,) that DO NOT affect the level of risk, level of IRB review, or the subject's willingness to participate DO NOT require further IRB review. However, when a proposed change increases the level of risk, there is the addition of funding, the investigator is required to submit proposed revisions through the iStar amendment application.

## 8.5 Review of Expedited Research

To submit a project for expedited review, the investigator must submit an expedited iStar application with appropriate attachments. IRB staff initially evaluates all submissions and may request changes/clarifications from the investigator. IRB staff then prepares a staff review that is forwarded to an expedited reviewer for review and approval. In the staff review the reasons why the submission meets expedited review criteria are noted by citing the appropriate expedited review category or summarizing the nature of the modification. The expedited reviewer is prompted to either concur or disagree with the staff recommendation for expedited processing and any related contingencies or necessary revisions.

The expedited reviewer has access to all necessary application materials in the iStar system, which includes the following:

- A completed [iStar](#) application with conflict of interest statement
- Investigator's or sponsor's protocol

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- Proposed informed consent document(s) and/or script as appropriate
- Surveys, questionnaires, or videotapes
- Relevant grant applications
- Recruitment materials and advertising intended to be seen or heard by potential subjects, including email solicitations

The expedited reviewer is responsible for evaluating the project to ensure that the rights and welfare of human subjects are protected and that all criteria for IRB approval have been met. The expedited reviewer is also responsible for determining whether the study can be approved with or without changes and whether clarifications are required.

The reviewer may request review of the research by an expert consultant for issues which require expertise beyond or in addition to that available on the IRB committee. A determination that the consultant does not have a conflict of interest is made.

The expedited reviewer may send requests for clarification directly to the PI, or can forward requests to the PI through the assigned IRB staff member. If the application requires modifications, the IRB correspondence identifies the modifications that must be made by the investigator before the study can begin. The investigator's response to correspondence arising from expedited review procedures need only be evaluated by the expedited reviewer. In the event that the expedited reviewer makes a recommendation that is not accepted by the investigator, the expedited reviewer has two options: (1) Accept the investigator's justification for not incorporating the recommendation and proceed with the approval of the study; or (2) Reject the justification and forward the submission to the next Full Board IRB meeting for further consideration of the issue.

All studies meeting criteria for approval under the expedited criteria must meet the requirements for informed consent or its waiver or alteration (see [Section 10.13 – Waivers of Informed Consent](#)).

If the study is approvable, the approval notice indicates expedited review procedures were followed and notes the expedited review categories under which the approval was granted.

Information or proposed changes submitted in an amendment, adverse event, sponsor notification, or sponsor notification may disqualify a study from being approved under

the expedited review procedure. In this situation, the study is forwarded to the full IRB for determination.

Expedited determinations and actions are distributed to all IRB members electronically and acknowledged by each committee.

### Expedited Reviewers

Expedited review may be carried out by the IRB Chair, Vice Chair, or by an experienced IRB member formally designated by the IRB Chair. To qualify as an expedited reviewer, the IRB member, according to the judgment of the IRB Chair, must have the experience and education required to conduct expedited review.

Expedited reviewers may exercise all of the authorities of the IRB, except for disapproving the research (a research activity may be disapproved only after review by the full committee). If the reviewer and investigator cannot agree on the changes required to secure approval, the application will be sent to the convened IRB for review. The reviewer may refer the application to the Full Board for review at any time.

Although expedited review requires fewer steps than full committee review, it is not a lesser review process. All of the requirements for the protection of human subjects are applied equally in expedited review and the same requirements for informed consent (or its waiver or alteration) apply to expedited categories of research.

If a research study is found to be ineligible for expedited review, it will be added to the next possible full committee meeting agenda for review.

## 8.6 Review of Full Board Research

To submit a project for Full Board review, the investigator must submit a Full Board iStar application. The IRB staff reviews the application to ensure it is complete, and if necessary, will request revisions and/or clarifications from the investigator. The staff review is available on iStar. The IRB staff schedules the study for the next available IRB meeting. The IRB Chair or IRB Director selects primary and secondary (and tertiary when applicable) reviewers. The reviewers' comments, questions, and contingencies are posted in the iStar system and discussed during the Full Board meeting. Study materials and reviewer comments are available to all committee members.

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The Full Board review process is described below:

- A majority of the members of the IRB and at least one non-scientist and one non-affiliated member (can be the same member with dual roles) must be present.
- If the required number of members is lost during a meeting no action may be taken until the quorum is restored.
- In order for a research project to be approved, it must receive the approval of a majority of the members present at the meeting.
- The IRB Chair reminds the IRB members of the requirement to disclose conflicting interests. The Chair polls the members present for any conflicting interests not previously declared or identified by IRB staff.
- IRB members cannot vote on a study if they are an investigator or member of the study team, if they significantly contributed to the design and conduct of the proposed study, if they meet the criteria for a financial conflict of interest, or if they have other interests that may affect their objectivity.
- A member with a potential conflicting interest may be invited to answer preliminary questions about a study, but then leave the meeting until the final vote is taken. The meeting minutes will record the name of any member who does not participate in the final vote on a study because of a conflicting interest.
- For studies involving subjects who may be vulnerable to coercion or undue influence, the IRB Chair, Director, or staff will ensure that one or more individuals who are knowledgeable about or have experience working with the subjects will review the study. These individuals may be current IRB members and/or consultants.
- For studies involving the recruitment of prisoners, the IRB Chair, Director, or Staff will ensure that a prisoner representative will be present at the meeting.
- A meeting may be conducted by conference call provided that each participating IRB member has received all pertinent material prior to the meeting and can actively and equally participate in the discussion of all protocols. Meeting minutes must clearly document that these two conditions have been satisfied and should specify which members were present via conference call.

- IRB meetings are scheduled at regular intervals appropriate to the amount of research requiring review and with sufficient frequency to ensure that the IRB can adequately oversee the progress of the research it has previously approved.
- Each protocol undergoing initial or continuing review will be discussed and voted upon separately.

### Full Board Reviewer Assignments

The IRB uses a "primary reviewer" system for review of all new research proposals at its convened meeting. Members will be assigned studies for which they will be responsible for providing a detailed review. Reviewer assignments are made with the following goals in mind: to ensure review by a member with appropriate expertise and to equally distribute assignments. The expectation is that each IRB member will be familiar with every study on a meeting agenda.

The number of assigned reviewers differs according to the nature of the submission and whether previous peer review(s) for scientific merit is available (such as review by the USC Clinical Investigations Committee (CIC), the USC Clinical Trials Unit (CTU), NIH cooperative groups, NIH study sections, sponsor review committees, and regulatory agencies such as the Food and Drug Administration). Peer reviews provide assurance that experts have evaluated the study and found it meritorious. Biomedical protocols that have not undergone peer/scientific review, additional reviewers with knowledge in the relevant discipline may be assigned to provide confidence in the scientific merit of the study. This process assures that in addition to all other review criteria scientific merit is properly addressed.

### Primary and Secondary Reviewer Responsibilities

The primary reviewer should be knowledgeable about the medical or social-behavioral issues relevant to the protocol. The primary reviewer performs a detailed review of the protocol in order to ensure that the study is appropriately designed to protect subjects and to achieve the stated goals of the project.

All reviewers are asked to upload a written review in iStar. In their written comments, reviewers identify human subjects protection concerns, explain the basis for raising those concerns, request modification to study documents, and ask for clarification or additional information. All assigned reviewers attend the IRB meeting and present their analysis to



the Full Board committee. If a reviewer is unable to attend the meeting, another assigned reviewer or the IRB Chair will present the review to the committee. Even if written comments are provided by the assigned reviewers, the board might choose to defer discussion of a protocol until a time when the assigned reviewer can attend the meeting and present concerns in person.

### Use of Consultant Reviewers

If the IRB Chair/Director determines that the IRB lacks the expertise necessary to review a particular study, the IRB will seek the services of an external consultant reviewer. An expert will be identified and invited to review the study as a consultant. The consultant will be required to disclose any possible conflict of interest to the IRB using the same criteria applied to investigators as outlined in [Section 13.6 – Investigator Conflict of Interest](#). Once it is confirmed that there are no actual or perceived conflicts of interest, a copy of the complete study submission and any reviews posted by the other reviewers will be sent to the consultant. The consultant will provide written comments to the IRB and may be invited to attend the meeting to discuss the protocol. The consultant cannot vote.

### Meeting Materials – Full Board

The IRB staff electronically distributes all meeting materials to IRB members or their alternates through iStar. To ensure adequate time for review, the meeting agenda, study documents, and minutes to be approved by the board are sent to members approximately seven days before the meeting. Meeting materials available to IRB members for new study submissions are listed below.

- iStar study application
- Previous correspondence from study team and IRB
- Study protocol
- Grant application (including budget)
- Sponsor's sample informed consent documents
- Drug and device brochures

## Chapter 8: Process of IRB Submissions

- Informed consent documents
- Child assent forms
- Surveys, questionnaires, and other instruments
- Recruitment materials
- HIPAA authorization forms and other documents required for medical research

A list of meeting materials for Continuing Review, amendments, and reportable event submissions are found in their respective sections in [Chapter 9 – IRB Considerations after Initial Approval](#).

### **Projects Needing Verification from Sources Other than the Investigator**

The IRB may determine that verification of required changes as well as study conduct need to be provided by sources other than the investigator. The IRB determines the appropriate sources and makes that part of the contingencies for approval. The criteria used by the IRB to make these determinations could include some or all of the following:

- Complex projects involving increased risk to subjects
- Projects conducted by investigators who previously have failed to comply with the requirements of the Health and Human Services (HHS) regulations or the requirements or determinations of the IRB, and
- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources

### **8.7 Sponsored Research and Ancillary Approvals**

Other university approvals may be necessary before a study can begin, depending on the type of funding and the type of study. Funding and contract agreements are negotiated through USC Department of Contracts and Grants, which includes the Clinical Trials Office. The IRB application will inform the reviewer and/or investigator that additional

approvals must be obtained. The ancillary approvals, encountered mostly with biomedical studies and less frequently with social behavioral studies, are described below.

### Funded Research

#### Department of Contracts and Grants

All research funds received from federal, state, and local government and/or private/foundations must be deposited with the Department of Contracts and Grants (DCG). The DCG:

- Serves as “gatekeeper” for acceptance, oversight and disbursement, and fulfilling government and university requirement
- Provides training and assistance to faculty and research administration staff
- Assists with proposal development, review, approval and submission
- Negotiates and accepts awards on behalf of the University
- Offers post-award administrative guidance
- Maintains the Sponsored Projects Data Information System (DCG Database)
- Provides support to University offices and committees in matters related to research policy and guidelines

#### Clinical Trials Office (Industry-funded)

The Clinical Trials Office (CTO) provides budget development and contract negotiation and execution for industry-sponsored research.

#### Medicare Coverage Analysis (MCA) and Consistency Review

CTO staff prepares the Medicare Coverage Analysis (MCA) for all clinical trials regardless of the funding source or Medicare eligibility. The MCA is used to identify and differentiate between costs that are study-related and those that are routine care. Routine care costs are independent from the study and would therefore be billed to Medicare, another insurer, or the subject. CTO verifies that the terms of “qualifying trials” are met before study costs are allocated.

The IRB staff works closely with CTO to ensure that language in the informed consent document and iStar application is consistent with the sponsor contract or Clinical Trial Agreement. CTO staff will modify and approve the language in the Financial Obligation and Compensation section of the iStar application as needed. This is accomplished using the “Review Consistency” activity.

If the investigator has addressed all the IRB contingencies before the CTO review is final, the IRB will approve the study but will not release the informed consent documents. The investigator cannot begin recruitment and enrollment until the CTO review is completed, the IRB confirms that the cost, injury, and compensation sections of the consent documents match the CTO language, and the IRB uploads the stamped consent documents in iStar. The IRB will notify investigators when the approved consent documents are uploaded and enrollment can begin.

### **Contract and Funding Agreements**

At USC, the Clinical Trials Office and the Department of Contracts and Grants are responsible for funding agreements. All institutional contract and funding agreements meet established standards and include:

- A written agreement addressing medical care for research participants with a research-related injury, when appropriate
- A written agreement stating that the sponsor promptly reports to USC findings that could affect the safety of participants or influence the conduct of the study (for studies in which sponsors conduct site monitoring visits or conduct monitoring activities remotely)
- A written agreement that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to USC, when the sponsor has the responsibility to conduct data and safety monitoring
- A written agreement, before initiating research, that addresses plans for disseminating findings from the research and the roles that researchers and sponsors will play in the publication or disclosure of results
- A written agreement that the researcher or USC will be notified of the results in order to consider informing participants, when participant safety could be directly affected by study results after the study has ended

### Ancillary Committee Reviews

Depending on the study, additional ancillary committee review and approval may be necessary before the study can begin. The IRB submission will trigger certain required approvals; however, some approvals are not linked to iStar and may be required after IRB submission depending on the study. Ancillary committees include:

- Institutional Biosafety Committee (IBC)
- Radiation Safety Committee (RSC)
- Stem Cell Research Oversight Committee (SCRO)
- Conflict of Interest in Research Committee (CIRC)
- Investigational Drug Pharmacy Services
- Pathology and Laboratory Services
- Clinical Trials Unit (CTU)
- Cancer Center Clinical Investigations Committee (CIC)

## 8.8 IRB Review and Determinations

### Full Board Review

At a convened meeting, after all reviewers present their analyses of the study, the discussion is opened to all members. During the discussion, other members note omissions, raise and/or comment on issues, request clarifications, and make suggestions to improve the readability of consent and recruitment documents. When all members have the opportunity to voice their concerns and no further discussion is necessary, the board votes upon the study and makes one of the following determinations:

### Approve

If the board determines that the study as written provides adequate protection of human subjects, the board will approve the study with no further changes.

### Approve with Contingencies

The contingencies under Approval with Contingencies are not contingencies that impact the regulatory determination for approval. If the board finds that the application is “approvable” with modifications, clarifications, or verifications, the board will approve the study with contingencies that can be verified by a designated reviewer. The IRB may require the following as conditions of approval:

- 1) confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted;
- 2) submission of additional documentation;
- 3) precise language changes to protocol or informed consent documents; or
- 4) substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

The IRB may designate the verification of satisfied contingencies to the IRB Chair, Vice Chairs, or an IRB member, without additional review by the Full Board. This process does not constitute an expedited review.

### Defer

If the board has serious concerns about the study, and/or requires significant modifications directly relevant to the criteria for regulatory determinations under 45 CFR 46.111 and/or 21 CFR 56.111, the board must defer a vote on the approval of the study. The subsequent response to request for significant modifications may not be reviewed using expedited procedures and must be reviewed by the Full Board. Examples of significant modifications include more than minor changes to the risks, research design and methodology, statistical analyses, data safety monitoring plan, provisions for protecting human subjects’ safety and privacy, and informed consent document(s).

### Table

If the board is unable to initiate a discussion of a study due to a lack of time, loss of quorum, or the absence of a reviewer, the board will table the discussion of the study for review at a subsequent meeting.

### Disapprove

If the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the board may disapprove the study.

An IRB member makes a motion for one of the above options; if another member of the IRB seconds the motion, the motion is voted upon. A majority of the members present at the meeting must vote in favor of the motion for passage [[45 CFR 46.108\(b\)](#) and [21 CFR 56.108\(c\)](#)]. Discussion and/or deliberations of each study on the meeting agenda continues until one of the above motions is passed.

## Expedited and Exempt Review

The IRB designated reviewer can make one of the following determinations:

- Determine that the study as written provides adequate protection of human subjects and approves the study (with no further changes). The IRB will approve a study only after determining that the proposed application contains sufficient information to address the criteria for IRB approval cited at [45 CFR 46.111](#) and [21 CFR 56.111](#).
- Find that the application is “approvable” after modifications, clarifications, or verifications and designate a reviewer (same reviewer, IRB Chair, Vice Chairs, another IRB reviewer, or IRB administrator) to verify that contingencies have been satisfied
- If the reviewer has serious concerns about the study, and/or requires significant modifications directly relevant to the criteria for regulatory determinations under

[45 CFR 46.111](#) and/or [21 CFR 56.111](#), the expedited reviewer can refer the study for Full Board review.

### Review of Response to Contingencies

When a study is approved with contingencies, the IRB designates a reviewer (same reviewer, IRB Chair, Vice Chairs, another IRB reviewer, or IRB administrator) to verify that contingencies have been satisfied.

- If the designated reviewer determines that the investigator has satisfied all conditions of approval, further IRB review is not necessary.
- If the reviewer determines that the investigator failed to adequately address the modifications requested by the IRB, the investigator's response may be returned to another member reviewer or to a Full Board meeting. The reviewer may request additional correspondence identifying outstanding concerns to be sent to the investigator by IRB staff.
- If the reviewer determines that the initial response and/or secondary correspondence from the investigator is inadequate, unacceptable, or raises new concerns, the study will be forwarded to the full IRB for further adjudication at the next possible IRB meeting.

Additionally, the following applies when changes to research are proposed after the IRB has approved the research with contingencies:

- If changes proposed are administrative/editorial in nature, no additional IRB review is needed and the changes can be reviewed as part of the verification process.
- If additional changes/procedures, which are listed in the expedited review categories under 45CFR 46.110, are proposed by the PI or designated reviewer, those changes may be reviewed by the IRB Chair/Vice-Chair/designated reviewer through an expedited review procedure.
- If changes are more than minor, increase risks to subjects, and/or impact any of the approval criteria under 45 CFR 46.111, those changes would require review by the full IRB committee.



This review process is applicable to review of response to contingencies after initial study submission, amendments, continuing review and reportable events.

### 8.9 IRB Correspondence and Investigator Response

#### IRB Correspondence

After each IRB meeting (or review by designated reviewer), the IRB staff forwards correspondence to investigators whose protocols were reviewed, notifying them of the action/status of their applications. The nature of the correspondence and the process by which an investigator's response is reviewed vary according to the decision made for the study.

- When the board (or reviewer) determines that the study as written provides adequate protections, the correspondence indicates the study is approved (with no further changes).
- When the board (or reviewer) finds that the application is “approvable” after modifications, clarifications, or verifications, the correspondence indicates the study is approved with contingencies.
- When a study is approved with contingencies, the IRB staff composes correspondence describing reviewers' comments and concerns and forwards it to the investigator. The investigator's response to the correspondence is then reviewed by the Chair/Vice Chair or designee.
- Correspondence indicates when the IRB or reviewer previously agreed that a response may be evaluated by a designated reviewer.
- When the IRB or reviewer has serious concerns about a study, or if significant modifications are required to ensure protection of human subjects, the correspondence indicates that the IRB will defer approval of the study until additional information is obtained from the investigator.
- For Full Board studies, when the board is unable to initiate a discussion of a study due to a lack of time or the absence of a reviewer, the correspondence indicates

the board will table the discussion of the study for review at a subsequent meeting.

- When the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the correspondence indicates the IRB's decision to **disapprove the study**. Investigator will have the opportunity to respond to the board in person or in writing [[45 CFR 46.109\(d\)](#) and [21 CFR 56.109\(e\)](#)].

IRB correspondence includes all the information required by federal regulations and/or guidance. Generally, IRB correspondence for Full Board review studies is approved by the Chair before it is sent to investigators.

IRB correspondence with IRB determinations and the IRB's action will be sent to the investigator [[45 CFR 46.109\(d\)](#) and [21 CFR 56.109\(e\)](#)]. When responding to the IRB's determinations or requests, the investigator may disagree with the board or reviewer, and provide written justification in support of their viewpoint. The IRB will then review the investigator's justification and make a determination. It should be noted, however, that the IRB has the final authority to approve or disapprove the research.

### Investigator Response

During the IRB review process, all requests for modifications or further clarifications from the IRB are documented in a letter and sent to the investigator by IRB staff via iStar. The investigator's response to the IRB correspondence is evaluated in accordance with the requirement set forth during the initial review (reviewed by the Full Board, reviewed by an expedited reviewer, or verified by an IRB staff member). All correspondence between the IRB and investigators is recorded and stored under the history tab in the iStar application.

If the investigator believes requirements imposed by the IRB are unduly restrictive of the proposed research, the investigator can contest the requirements to the IRB. The investigator can outline the reasons why the proposed research procedures are already in compliance with USC policy and the applicable federal regulations and request that the IRB reconsider the requirement. If the IRB rejects the appeal, the investigator must comply with the IRB's restrictions or the research will not be approved. No other entities or officials at USC may override the IRB's decision to disapprove a study.

Other institutional entities or officials may determine that a study approved by the IRB cannot be conducted. Among the reasons for disapproval are issues of inadequate resources or university sensitivities.

### 8.10 IRB Meeting Schedules

#### IRB Meeting Schedule for Biomedical Study Review

HSIRB 1 meets the first and third Thursday of each month. HSIRB 2 meets the second and fourth Thursday of each month. HSIRB 3 meets on the first and third Tuesday of each month. A calendar for submission and review dates is available on the HSIRB website <http://oprs.usc.edu/hsirb/meetings/>.

#### IRB Meeting Schedule for Social Behavioral Study Review

The IRB reviews social and behavioral studies monthly. A calendar for submission and review cut-off dates is available on the website: <http://oprs.usc.edu/upirb/meetings/>.

### 8.11 Additional IRB Submissions

In addition to the IRB submissions described earlier in this chapter, there are other IRB submissions applicable to human subjects research. These IRB submissions include Continuing Review, Amendments, Reportable Events, and Reports. These submissions are not discussed further in this chapter as they are described in [Chapter 7 – Types of IRB Submissions](#) and discussed as part of the IRB submission process in [Chapter 9 – IRB Considerations after Initial Approval](#).

#### Primary Investigator and Self-experimentation

Application of submission for USC IRB review is required for human subjects studies entailing self-experimentation.

USC policy does not distinguish between self-experimentation and research on subjects who are recruited for a specific project. As part of its commitment to the protection of the rights and welfare of individuals participating in research, USC's Research Protection

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Program requires investigators who wish to act as participants in their own studies to submit for IRB review and approval - following standard procedures as outlined in the IRB policy. All human subject research must be reviewed to assure safety of those involved and the integrity of the research at the university. While researchers may be aware of the risks of self-experimentation, they may also be more willing to accept risks that are ill-advised. Application for review with the IRB office allows a neutral third party to raise concerns and/or propose measures to promote the welfare of researchers.

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## **Chapter 9**

# **IRB Considerations after Initial Approval**

This chapter describes investigator reporting requirements after a research project is approved. It covers amendments to approved research, continuing review, expiration of IRB approval, adverse events and unanticipated problems, project closure, record keeping, and publications. Only the major reporting responsibilities of investigators are described here. There may be additional responsibilities placed on the Principal Investigator by a sponsor, regulatory agencies, or the IRB. For more in-depth information about investigator reporting requirements, refer to the referenced sections in this manual.

### **9.1 Amendments – Changes to Research after Approval**

The IRB requires investigators to submit modifications to previously approved studies through an amendment in iStar. IRB approval of the amendment must be granted before any changes in research activities are made. When a change is necessary to eliminate apparent immediate hazards to the research subjects or others, the IRB must be informed and the investigator must submit a Reportable Event in iStar “Protocol Change Initiated to Eliminate Immediate Hazard” to the IRB [promptly](#) (within 10 days). (Please see [“Providing Significant New Information Involving an Apparent Immediate Hazard”](#)) Subsequently, an amendment with revised study documents (such as an updated consent form and updated protocol) must be submitted to the IRB within 30 days. The Principal Investigator must notify the sponsor as required by the sponsor or FDA. The IRB will review the change to determine that it was consistent with ensuring participants’ continued welfare. The IRB approval letter sent to the investigator outlines this responsibility.

### Significant New Information / Findings

Significant New Information/Findings relating to protocol changes should be provided to participants when such information might relate to their willingness to continue to take part in the research. This new information, termed Significant New Information/Findings can be provided to subjects in various ways depending on urgency (refer to [Section 10.15 – Providing Significant New Information and/or Findings \(SNIF\) to Participants](#) for more information).

Investigators should be aware that certain modifications may require changes in the budget or contract agreements with the sponsor or funding agency. Investigators should contact the Clinical Trials Office and/or the Department of Contracts and Grants to discuss the need for budget or contract changes.

Investigators should also be aware that the original expiration date of a study does not change when an amendment is approved by the IRB. Expiration dates change only at the time of continuing review.

### Materials Available to the IRB for Amendment Reviews

The electronic IRB application contains the following information that is available to the IRB for review of amendments:

- iStar Amendment Application, including a description of the proposed changes and any revised documents
- Correspondence from study team
- All previously reviewed documents

The entire study history is available to members in the iStar application.

### Levels of Review for Amendments

Amendment submissions may receive full committee or expedited review, according to the nature of the proposed changes and their effect on the risk/benefit ratio.

### Full Committee Review of Amendments

If the changes proposed to the protocol are substantial or if the changes alter the risk/benefit ratio of the study, the amendment must be reviewed by the full IRB.

Examples of such changes are an increase in dosage of an investigational drug, a significant increase in the risks to subjects, addition of a procedure that is greater than minimal risk to subjects (such as addition of an x-ray for research purposes), addition of a new subject population (such as adults who are not competent to consent or children), or significant changes in study design.

As in their initial and continuing review, members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111.

### Expedited Review of Amendments

If proposed changes to a protocol are *minor*, an amendment may qualify for expedited review. The IRB defines “minor modifications” as any change in the previously approved protocol that does not deviate significantly from the requirements for approval during the previous IRB review. Modifications are considered minor when all the following criteria are met:

- the change does not significantly alter the risk/benefit ratio the IRB relied upon to approve the protocol
- the change does not significantly affect the safety of subjects
- the change does not involve the addition of procedures, interactions or interventions that add significant medical, social or psychological risks
- the change does not involve addition of a vulnerable population in research not otherwise eligible for expedited review, and
- the change does not significantly alter the scientific question or the scientific quality of the study

Examples include editorial changes to the protocol or consent form, the addition of an investigator or Faculty Advisor, change in the number of study subjects to be enrolled,



and the addition of a procedure that does not pose more than minimal risk to study participants (such as the addition of a small-volume blood draw).

Expedited review is conducted by experienced IRB members designated by the IRB Chair under [45 CFR 46.110 \(b\)\(2\)](#). Expedited reviewers evaluate the proposed changes to ensure compliance with review criteria [45 CFR 46.111](#) and [21 CFR 56.111](#).

### Changes in Study Personnel

Study personnel changes (with certain exceptions) can be made to the IRB application without submitting an amendment. To do this, research staff can select the “Edit Study Personnel” activity in the iStar study workspace and add or delete study personnel. Any study personnel added to a study must have current human subjects training. However, an amendment must be submitted to the IRB when changing a Principal Investigator or Faculty Advisor, adding Co-Investigators, or adding any study personnel who will obtain consent.

For information on submitting amendments to research determined to be exempt, see [Section 8.5 – Review of Exempt Research](#).

## 9.2 Continuing Review

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year after the study receives initial IRB approval [[45 CFR 46.109\(e\)](#)]. Subsequent IRB review is called “continuing review.”

Unless the IRB determines otherwise, continuing review is no longer required for research determined minimal risk, not FDA regulated and not federally funded.

### Objectives of Continuing Review

The IRB performs continuing review to systematically monitor previously approved research and document that the requirements imposed by the IRB during the initial review and approval of the protocol continue to sufficiently protect subject safety and welfare. A second objective of continuing review is to confirm that all information presented to subjects is complete, accurate, and up-to-date. The investigator must submit a continuing review application through iStar which includes:

## **Chapter 9: IRB Considerations after Initial Approval**

- The relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval
- The number of human subjects accrued. If the study has multiple cohorts or phases, subject accrual must be explained in more detail.
- An updated abstract
- A description of adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, protocol deviations/errors, or complaints about the research
- A summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation
- A description of interim findings or benefits and the progress of the study
- A current risk-benefit assessment
- Any new information relevant to any subject's participation since the IRB's last review
- The current informed consent/assent document(s), information sheet, and/or verbal script, as appropriate (if subject enrollment is open)
- Any relevant multi-center trial reports (Data Safety Monitoring Board, audits,)
- Any investigator/institutional conflict of interest
- Any incidental findings in fMRI studies occurring at the Dornsife Neuroimaging Center
- Verification of funding information, study personnel, and study locations
- If the study is closed to enrollment and the current study status is not data analysis only, the reason for accrual closure must be provided
- If the study status is "Enrolling New Subjects" and no new subjects were enrolled (or fewer than expected) since the last progress report, an explanation must be provided

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In addition to the Continuing Review application described above, the IRB has the following materials available to consider for Continuing Review approval:

- Correspondence from study team
- Currently approved iStar study application, including all previously reviewed documents
- Study protocol
- Grant application (including budget)
- Sponsor's sample informed consent documents
- Drug and device brochures
- Informed consent documents
- Child assent forms
- Surveys, questionnaires, and other instruments
- Recruitment materials
- HIPAA authorization forms and other documents required for medical research
- All reports of adverse events, including:
  - Protocol deviations/exceptions
  - Participant complaints
  - Unanticipated problems
  - Data Safety Monitoring Board (DSMB) or monitoring/auditing reports, including any relevant multi-center trial reports
  - IDE annual reports from sponsors

As in their initial review, IRB members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111.

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To address the criteria for IRB approval, a copy of the currently approved application is maintained in the iStar online submission and tracking system. The iStar application is updated with each approved modification and so represents the current parameters under which IRB approval is granted.

The IRB has developed comprehensive reviewer guidelines/checklists to assist IRB members and IRB staff in performing thorough reviews. These forms can be found on OPRS website: <https://oprs.usc.edu/irb-review/checklists-for-irb-review/>. (also refer to [Appendix B](#)).

Finally, the Board determines which projects need verification from sources other than the investigators confirming that no material changes have occurred since previous IRB review [[45 CFR 46.103\(b\)\(4\)\(ii\)](#) and [21 CFR 56.108\(a\)\(2\)](#)]. The criteria used by the IRB to make these determinations could include some or all of the following:

- Randomly selected projects
- Complex projects involving unusual levels or types of risk to subjects
- Projects conducted by investigators who previously failed to comply with the requirements of Health and Human Services regulations or the requirements or determinations of the IRB, and
- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.

### Levels of Continuing Review Submissions

Continuation submissions may receive full committee or expedited review according to the status of the research. For additional guidance, refer to the:

- IRB Continuing Review for Full Board Studies [worksheet](#)
- IRB Requirements for Continuing Review after Enrollment and Data Collection are Completed [worksheet](#)

### Full Committee Review

Studies that do not meet the criteria for expedited review and belong in one of the following categories must undergo full committee review:

- Actively enrolling new subjects and/or providing research-related interventions to previously enrolled subjects.
- Subject accrual is complete and previously enrolled subjects continue to receive research-related treatment/interventions.

### Expedited Review

The Chair/Vice Chairs and IRB members designated by the Chair serve as expedited reviewers of the IRB. In this capacity, these members perform expedited review of continuations that fall into one of the following categories:

- Research permanently closed to the enrollment of new subjects. All subjects have completed all research-related interventions and the research remains active only for the long-term follow-up of subjects.
- Research previously approved by the fully-convened IRB where no subjects have been enrolled and no additional risks have been identified.
- Research in which the remaining activities are limited to data analysis only.
- Research previously reviewed by the IRB via expedited review procedures.
- Research, not conducted under an investigational new drug application or investigational device exemption, where categories (2) through (8) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

### Continuing Review Determinations

#### Approved with Contingencies\*

A continuing review application is “approved with contingencies” when the IRB requires as a condition of approval that the investigator make specified changes to the application, confirm specific assumptions about the study, or submit additional documents.

If the research expires before the contingencies are reviewed and approved, all research activities must stop until approval is obtained, unless it is determined by the IRB to be in the best interests of already enrolled subjects to continue participating in the research. However, new subjects may only be enrolled after all contingencies are satisfied. For FDA-regulated research, the IRB also permits the study to continue while the investigator addresses outstanding contingencies, consistent with [FDA guidance on continuing review](#).

If a researcher does not submit a continuing review application to the IRB or the IRB has not approved the study by the expiration date, all research activities stop unless it is determined by the IRB to be in the best interests of already enrolled subjects to continue participating in the research. If continuing review contingencies have not been satisfied by the investigator and a subsequent amendment is submitted for review, the IRB may require that the investigator satisfy continuing review contingencies before the IRB will approve the amendment.

If the review of responsive materials from investigators requires medical, scientific, or other technical expertise, the IRB should designate an individual with the appropriate expertise to review the investigator response. Typically, this would be the IRB Chairperson, another IRB member, or an expert consultant.

If the review of responsive materials from investigators is limited to verification of verbatim changes or submission of a specific document, the IRB could designate an IRB administrator to review the investigator response. This verification process is not equivalent to approval of minor changes under an expedited review procedure.

*\*At USC, contingencies and conditions are used interchangeably.*

#### Approval for Follow-up Only

Continuing review is not required for research only conducting follow-up activities unless the research is subject to FDA regulation. “Follow-up only” occurs when subject

accrual and research-related interventions have been completed, although previously enrolled subjects may continue to be monitored for safety and outcomes as detailed in the approved protocol. When “follow-up only” approval is granted, the approved consent form(s) will not be issued.

### **Approval for Data Analysis Only**

Continuing review is not required for research conducting “data analysis only” unless the research is subject to FDA regulation. A research project approved for “data analysis only” occurs when subject accrual and all follow-up activities at USC have been completed; however, the protocol remains active for data analysis purposes only. Protocols should remain open for data analysis only when the investigator intends to continually analyze the data for potential dissemination through journal articles or poster presentations related to the stated objectives in the currently approved protocol.

### **Investigator Responsibilities**

Investigators are required to submit the continuing review application through the IRB Submission Tracking and Review system (iStar). The application should be submitted one to two months before the study expiration date to allow for timely continuing review and approval. It is the principal investigator’s responsibility to submit an application for continuing review in sufficient time to permit the IRB to review and approve the application prior to its expiration date.

If the principal investigator does not submit a continuing review application before the expiration date, all research activities must stop.

To assist investigators in fulfilling the requirement for continuing review, the IRB sends expiration notices through iStar to the investigator, faculty advisor, and study contact person at 90, 60, 45, and 30 days prior to expiration. If investigators do not forward a completed application for continuing review at least 30 days before the protocol expiration date, the IRB cannot guarantee that the application will be reviewed before the date of expiration.

It is the investigator’s responsibility to ensure that approval for an active protocol remains current. The IRB expiration date can be found on the main study page of the approved protocol in iStar, in the IRB approval letter, and in the expiration notices.

### 9.3 Project Closure

When a study ends, is closed, or is canceled for any reason, a final report must be submitted to the IRB through iStar either by submitting a continuing review application or by selecting the “Close Study” button (for selected studies). This report notifies the IRB that continuing review of the study is no longer needed.

A research project is closed when subject accrual, subject follow-up and data analysis are completed at USC. Once the investigator or the IRB has closed a study, no further research activity, including data analysis, may occur. It is permissible for a study to be closed at USC when it is still open to accrual at other sites. In the event that a serious adverse event or an unanticipated problem occurs at a non-USC site after the closure of the study at USC, the USC investigator is required to submit the SAE report via iStar as outlined in [Section 20.1 – Adverse Events](#).

If no subjects have been enrolled in a study for a period of three or more years, the IRB may require the investigator to close the study unless there are extenuating circumstances for keeping a study open (for example, when the study is about a rare condition).

### Studies in Data Analysis Only

Studies that are conducting “data analysis only” and not FDA regulated are not required to submit continuing review.

### 9.4 Expired Projects

If the investigator does not submit a continuing review application through iStar by the current expiration date, the investigator is notified by e-mail that IRB approval has expired. The email includes a notice that all study-related activities must cease (including recruitment, advertisement, enrollment, interventions, interactions, collection of private identifiable information, and data analysis).

If IRB approval expires, the investigator may request IRB permission to continue if stopping interventions may place study subjects at risk



Investigators can notify the IRB and request permission to continue study intervention after IRB expiration using the request for treatment extension activity in iStar. An IRB Chair or Vice Chair will review and acknowledge the request. The investigator will receive an acknowledgment message through iStar. Other research activities (such as recruitment, enrollment, and data analysis) may only be resumed after the IRB approves the continuing review application.

If research interventions have been conducted beyond the expiration date, the PI must notify the IRB immediately.

### 9.5 Data Safety Monitoring Report

A data safety monitoring report is an interim analysis that is conducted by a committee (such as a Data Safety Monitoring Board or a Data Monitoring Committee) independent of the research team and the IRB. The committee looks at data as it is being collected to determine if unexpected risks and safety issues have occurred. The committee may recommend alterations in the protocol, termination of a study for reasons of obvious benefit or harm, or continuing the research without change. Additional information is found in [Chapter 21 – Data Safety Monitoring](#).

At USC, this report is submitted to the IRB through the iStar reportable event application.

### 9.6 Protocol Deviation or Error

A protocol deviation refers to those occasions when protocol required procedures are accidentally or intentionally not met. The determination as to which deviations or errors must be reported to the IRB is driven by sponsor/monitor requests or concerns of the principal investigator or research staff. There is no regulatory language that defines which deviations meet the level of required reporting. When the choice is made to report a deviation, it should be submitted through iStar as a reportable event.

### 9.7 Noncompliance

Noncompliance is a generic term that is used to describe behavior that is not expected or acceptable and may or may not be intentional. Noncompliance may require action by the IRB or the Institution. The IRB will determine whether an action constitutes noncompliance and whether the noncompliance is serious and/or continuing noncompliance.

Potential noncompliance with [45 CFR 46](#), FDA regulations, or institutional requirements should be reported promptly to the IRB. For more information, see [Section 20.8 – Procedure for Handling Reports of Alleged Noncompliance](#).

### 9.8 Reportable Events

Federal regulations require written procedures for prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others.

The reportable events policy is established to comply in part with the regulatory requirement in 45 CFR 46 and FDA 21 CFR 56. For more information, see Chapter 20 – Reportable Events, Noncompliance, Suspensions and Terminations.

### Adverse Events

Adverse events that are unexpected, related or possibly related, and are either serious or place subjects or others at a greater risk of harm than was previously known or recognized, must be reported to the IRB through iStar. Reporting to the USC IRB must be done as soon as possible, but not later than 10 working days of the investigator becoming aware of the event.

The FDA defines adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” in the [Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans](#).

OHRP defines adverse events as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research” in the [“Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.”](#)

### Unanticipated Problems Involving Risks to Subjects or Others

The term **unanticipated problems involving risks to subjects or others (UPX)** is found (but not defined) in the HHS regulations at 45 CFR 46.103(b)(5), and is found in the Food and Drug Administration regulations at 21 CFR 56.108(b)(1).

An unanticipated problem involving risks to subjects or others (UPX) includes any incident, experience, or outcome that meets **all** of the following criteria:

- ***unexpected*** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- ***related or possibly related*** to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and
- suggests that the research ***places subjects or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) ***than was previously known or recognized***

Events that meet the definition of UPX (see above) must be reported to the IRB. The method for submitting a UPX report is through the reportable event application in the iStar system.

### Adverse Device Effects

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” [[21 CFR 812.3\(s\)](#)].

Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

See the [Chapter 20 - Reportable Events, Noncompliance, Suspensions, and Terminations](#) for more information.

### Materials Available to the IRB for Reportable Event Reviews

IRB reviewers have access to the entire iStar study file and study history when reviewing reportable events. The iStar Reportable Event application may include associated documents such as Medwatch reports, other reports of the adverse event, or other supporting documents.

## 9.9 Participant Complaints

A participant complaint is an expression of dissatisfaction by the participant (or his/her representative) that may or may not involve a breach in human subjects rights or research ethics. Participants may choose to report complaints to the study team, the IRB, or a third party (such as hospital administration). Therefore, it is important that during the consent process, subjects receive consent forms and information sheets that include investigator and IRB contact information so that participants have resources to ask questions about the study and report complaints.

At USC, subject complaints must be reported by the study team in iStar using the “Participant Complaint” form in the “Reportable Events” application. The report should

## Chapter 9: IRB Considerations after Initial Approval

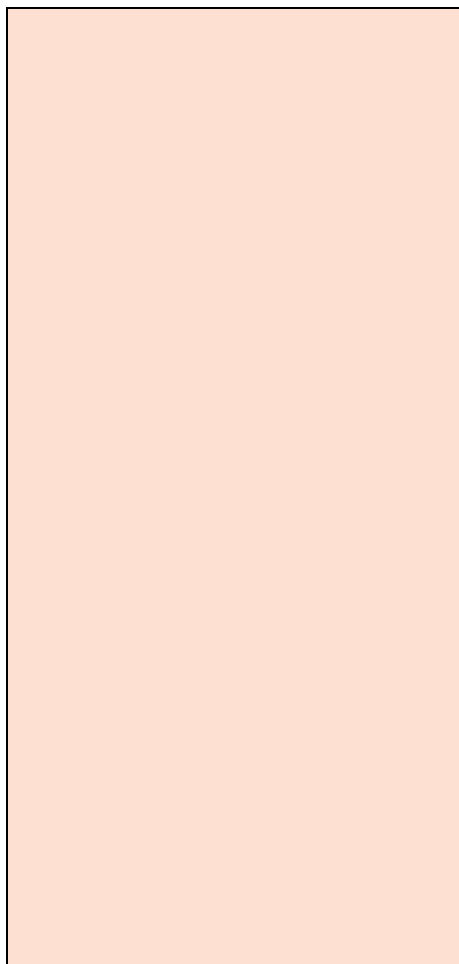
be specific and include: date of the complaint, event description, relation to the study, determination of whether the complaint involves increased risk to study participants, explanation of how a similar event will be prevented in the future and supporting documentation if applicable. Alternatively, the study team can choose to contact the IRB directly to discuss the participant complaint. Complaints reported to OPRS, Office of Compliance (OOC) or third parties will be subsequently reported to the IRB. When the IRB receives a participant complaint from one of these sources or directly from the participant, the IRB staff or Director will be responsible for documenting the complaint in iStar.

Once all the information is received, the IRB will determine if any further action is necessary. The IRB will provide written correspondence to the subject and principal investigator with their determination and justification for actions taken. The determination and outcome of the complaint will be documented in iStar by the IRB.

If the IRB office suspects there may be potential non-compliance, the IRB will initiate the process as outlined in [Section 20.8 – Procedure for Handling Reports of Alleged Noncompliance](#). For additional information regarding subject complaints, refer to [Section 22.1 – Participant Complaints](#).

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# Chapter 10

## Informed Consent Requirements

Investigators are required to obtain informed consent as a legal and ethical obligation. This chapter discusses the process of consent, the elements of consent, and legal requirements involved when obtaining informed consent from subjects.

No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or to appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the Institution or its agents from liability for negligence.

### 10.1 The Process of Consent

Informed consent is more than a form; it is a process. Information must be presented to participants so that they can voluntarily decide whether or not to participate in research. Prospective subjects must be provided with the information that a “reasonable person” would want to have in order to make an informed decision and subjects must be provided the opportunity to discuss that information. The informed consent form must be written in “lay language” to ensure participants can understand its content. The amount of information contained in the consent and the manner of presentation is related to the complexity and risk involved in the study. The consent form serves to document the basis for consent and also serves as future reference for study subjects. (See [Appendix F](#) IRB Forms and Templates)

While the informed consent process is prospective and takes place before research activity are conducted, consent should also be an ongoing interaction between the investigator and the research subject for the duration of the study. Subjects must be informed about significant new information or findings that develop during the course of the study that may affect their willingness to continue participation. Refer to [Section 10.15 – Providing Significant New Information/Findings \(SNIF\) to Participants](#) for more information.

The informed consent form must be signed before any study procedures begin. The investigator or research staff verbally explains the purpose and procedures involved in the study. The research staff answers questions and provides information to allow the subject



## Chapter 10: Informed Consent Requirements

to make an informed decision with ample time to consider participation. Thus, investigators should consider whether obtaining consent on the same day that study procedures begin provides participants enough time to consider participation.

The consent process must be free of coercion or undue influence. If an investigator has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between the parties.

The consent document should be revised when new information becomes available or when changes will improve the consent process. Any proposed changes to an IRB-approved informed consent form must be reviewed and approved by the IRB before changes are implemented (unless the change is necessary to avoid immediate harm to subjects or others). Refer to [Section 9.1 – Amendments – Changes to Research after Approval](#) for additional information.

### Consent and Assent

Only competent adults can give legally effective informed consent to participate in research.

Minors and those individuals who are not competent to give consent should be asked for their agreement to take part in the research. Assent is a knowledgeable agreement to participate in a research project.

Adequate provisions should be made for soliciting the independent, non-coerced assent from minors/children or cognitively-impaired persons who are capable of knowledgeable agreement. In general, the IRB recommends that children ages seven and older and most cognitively-impaired adults be given the opportunity to assent. In cases where assent is obtained from a minor or cognitively-impaired subject, permission must also be obtained from a legally authorized representative. The legally authorized representative may be a parent, a court-appointed guardian, or the court.

Special attention must be given to state law regarding attaining the age of majority (18 years of age) and situations involving emancipated minor subjects. Refer to [Section 10.14 – Child Assent Special Requirements](#) for more information.

### 10.2 California Experimental Subject's Bill of Rights

The California Experimental Subject's Bill of Rights is a document that is legally required for all studies involving a medical experimentation\* in the state of California. And the goal is to provide subjects with a clear statement of their rights as study subjects.

California law requires that the Experimental Subject's Bill of Rights should remain a separate document from the informed consent form. It must be attached to the front of the informed consent form as illustrated in the Informed Consent Template and Instructions available on the [OPRS](#) websites. In addition, the copy is to be dated and signed by the subject or the subject's legally authorized representative. The subject or subject's legally authorized representative is given a copy of the Experimental Subject's Bill of Rights before giving consent to participate in any medical experiment.

The California Experimental Subject's Bill of Rights must be provided to the subject or subject's legally authorized representative in his or her language during the consent process. This also applies when a Short Form is used in the consent process. The Bill of Rights is available in various languages on the [OPRS](#) websites.

\* A medical experiment is defined under section [24174](#) of the California Health and Safety Code as follows: “(a) The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, as defined in Section [109920](#) or [109925](#), electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the subject or otherwise directly benefiting the subject; (b) The investigational use of a drug or device as provided in Sections [111590](#) and [111595](#); (c) Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject.”

### 10.3 HIPAA Research Authorization Form

For research involving protected health information (PHI), a current **Health Insurance Portability and Accountability Act** (HIPAA) research authorization form must be signed. The subject or legally authorized representative must sign and date the

authorization form. If the subject is a minor (under 18 years old), a parent will sign the HIPAA authorization form. HIPAA authorization templates can be downloaded from the following website: <http://oprs.usc.edu/rules/hipaa/>.

Investigators should refer to “Instructions for Completing HIPAA Research Authorization Forms” provided by the USC Office of Compliance. This instruction sheet explains what sections can and cannot be changed. If additional changes to language in the HIPAA Authorization are required, these changes must be submitted to the Office of Compliance for approval before they are used. For additional information regarding HIPAA Privacy Regulations, refer to the Office of Compliance at <http://ooc.usc.edu/hipaa-privacy-regulations>.

California Law requires the HIPAA Authorization to remain as a separate document from the informed consent form.

### **10.4 General Data Protection Regulations (GDPR) European Union Privacy Laws**

The General Data Protection Regulation (GDPR) effective 5/25/2018 has been designed to harmonize data privacy laws across the European Union (EU). These regulations have the potential to affect clinical research and other scientific research activities conducted by USC. Investigators should be aware that research involving “personal data” about individuals in the EU/EEA (European Economic Area) must comply with the GDPR.

In addition to entities established in the EU/EEA, the GDPR applies to the processing of “personal data” by a controller or processor who is not physically established in the EU/EEA when the processing is related to (a) the monitoring of behavior of research subjects who are in the EU/EEA, or (b) offering goods or services to research subjects in the EU/EEA. The U.S.-based use and processing of “personal data” that has been collected in the EU/EEA, for clinical or other research purposes is subject to the GDPR. The regulations also apply to “Personal data” collected for clinical or other research purposes, from research subjects who have relocated to reside in the EU/EEA.

GDPR defines “Personal Data” as “any information relating to an identified or identifiable natural person” who is in the EU/EEA, regardless of the individual’s EU/EEA citizenship status. EU/EEA data protection authorities deem data to be de-

## Chapter 10: Informed Consent Requirements

identified if there is no reasonable means through which someone who has access to the data could use the data to re-identify an individual who is the subject of the data.

Individually identifiable data collected from an EU/EEA citizen at a location in the United States will be subject to United States law and not GDPR, unless the data was solicited from an individual while in the EU/EEA, or the organization continues to monitor the EU/EEA citizen after the citizen returns to the EU/EEA. More information is available at: <https://oprs.usc.edu/policies-and-procedures/gdpr/>

### **IRB will assure that proper consent appears on GDPR qualified studies:**

A valid consent to process an individual's Personal Data for research purposes under GDPR must be freely given, specific, informed and unambiguous agreement to the processing. GDPR permits an organization to rely upon consent from research subjects as a lawful basis for processing Personal Data for research purposes.

IRB Templates will be updated to include the necessary language to meet the GDPR requirements.

This information is:

- The period for which the data will be stored.
- Any projected future use of the data.
- The fact that consent may be withdrawn and data will be deleted.

Primary investigators are responsible for discerning whether their study data collection demands adherence to the General Data Protection Regulation (GDPR). For guidance refer to: NIH Recommendations: <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-implementation-of-the-european-unions-general-data-protection-regulation-and-its-impact-on-human-subjects-research/index.html>.

## **10.5 Required Elements of Informed Consent**

Informed consent Templates provide sample language, instructions, and guidance. The templates include the [HSIRB Informed Consent Template](#) which is to be used when there is no model template provided by an industry sponsor or cooperative group. The [Industry Sponsor, Cooperative Group, or External IRB Informed Consent Template](#) is to be used when a model consent form is provided by an industry sponsor, cooperative group or

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external IRB. The use of the latter template should require less editing and allow for a more expedient processing for industry sponsored studies. By following the consent templates, investigators ensure that the basic and additional elements of consent are included as required by federal regulations. Federal regulations ([45 CFR 46.116](#) and [21 CFR 50.25](#)) specify eight basic elements and six additional elements of informed consent described below. Informed consent templates for social behavioral studies, non-medical research and neuroimaging using fMRI can be found at the following link: [Social Behavioral Research – Informed Consent Templates](#)

### Basic Elements of Informed Consent

The following information shall be provided to each subject or the legally authorized representative.

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others that may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

### 10.6 Additional Elements of Informed Consent

Six additional elements of informed consent may apply, depending on the nature of the study [[45 CFR 46.116\(b\)](#)]. When appropriate, informed consent forms must also include one or more of the following elements:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;
- The approximate number of subjects involved in the study.

### Other Information to be Included in Consent

#### Compensation

The informed consent form should describe any compensation available to subjects. This may include payment for participation and reimbursement for expenses such as parking fees, travel expenses, and childcare incurred during the study. The consent form should

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explain how and when subjects will receive payment. In alignment with [Food and Drug Administration \(FDA\) recommendation](#), USC encourages the adoption of a pro-rated payment system whenever possible. The nature, amount, and method of payment must not constitute undue inducement to participate. The payment alone should not serve as sufficient inducement for the subject to volunteer.

If subjects will receive more than \$600 per year for taking part in one or more research studies, the consent form should explain that subjects may receive an Internal Revenue Service (IRS) Form 1099. The \$600 per year amount does not include reimbursements for expenses.

### **Academic Credit**

If payment will be in the form of academic credit that will be awarded for research participation, the amount and type of credit should be clearly stated as well as any required conditions for credit.

### **Commercial Products**

Investigators are required to inform subjects in the informed consent form if their biological human materials (such as tumor tissue, bone marrow, or blood) may be used to establish a commercially useful product (such as a cell line). Subjects should also be informed that they will not receive payment for any commercial product developed from their specimens.

### **Sponsor or Funding Agency Identification**

If applicable, subjects should be told what entity is funding the research (such as the drug company, device manufacturer, federal agency, or foundation). This information should appear in the introductory section of the consent form.

### **Conflict of Interest**

The research team must disclose all financial or other personal considerations that compromise, or have the appearance of compromising, professional judgment in proposing, conducting, supervising, or reporting research. Conflicts include financial, non-financial and institutional interests.

### Disclosure of Incidental Findings

The consent form must clarify whether or not subjects will be informed about information obtained but not sought as part of the research project.

### Consent of Pregnant Partner

Sponsors of drug studies may provide a sample informed consent for pregnant partners. This consent form is used if a female partner of a male participant becomes pregnant during the study and there are potential risks to the woman or fetus from exposure to the drug. The purpose is to obtain medical information about the partner's pregnancy and birth outcomes to learn more about the risks of the study drug.

If a pregnancy occurs in a partner of a USC participant, the investigator should notify the IRB.

## 10.7 Who May Conduct the Informed Consent Process

Who may conduct the informed consent process is determined by institutional policy and the risks and nature of the study. The following is the USC policy on who can conduct the informed consent process for human research studies:

- Individuals who are knowledgeable about the protocol must obtain consent from subjects for participation in a study. Specifically, they must be able to describe the purpose, procedures, benefits, risks, and alternatives to participation in the study. They must be able to answer subjects' questions about the protocol and about risks of the research procedures and alternatives.
- For studies involving medical procedures, the person obtaining consent should be licensed and privileged to conduct those procedures. Sometimes more than one person on the research team participates in the consent process. For example, study coordinators may describe the study procedures and a physician investigator may discuss specific issues related to the medical interventions and potential alternative treatments.



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- All individuals who participate in the informed consent process must first successfully complete the online USC Human Subjects Education Program through the Collaborative IRB Training Initiative ([CITI](http://opr.s.usc.edu/education/citi/)). More information on CITI is available at the following website <http://opr.s.usc.edu/education/citi/>.
- The PI must identify all individuals who will obtain consent and attest that they fit the above criteria. The PI is ultimately responsible for ensuring that ethically and legally valid consent is obtained from all research subjects.
- The investigator or other person obtaining informed consent must sign the study consent document(s) on the signature line labeled “Person Obtaining Informed Consent”.

### 10.8 Legally Authorized Representative

Legally Authorized Representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedures involved in research. California law specifies who can be the Legally Authorized Representative and provide consent when a subject is not able to provide informed consent.

For studies involving cognitively-impaired adults, consent guidelines and the use of legally authorized representatives are governed by [California Health and Safety Code Section 24175](#). For more information, refer [Section 14.4 – Cognitively-Impaired Persons](#). If studies relate to the subject’s cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions, consent must be sought from the surrogate decision makers based on the order defined in California Law [CA Health and Safety Code 24178](#).

If the person from whom assent is sought refuses, the person should not be enrolled, even if the parent or authorized representative gives permission. Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or authorized representative does not give permission

### 10.9 Documentation of Informed Consent

The purpose of an informed consent form is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the IRB-approved, written informed consent form which is signed and dated by the subject, or the subject's legally authorized representative, at the time of consent. A copy of the informed consent form must be given to the subject. Unless the investigator has requested a waiver of documentation of consent, the subject's signature on an informed consent form is required prior to beginning any study procedures.

Information given to the subject or the representative must be in a language understandable to the subject or representative.

When deception is used as a technique in research, there should be a prompt and complete debriefing of the subjects. Debriefing may include explaining the research, and if possible, providing the opportunity for withdrawal of personal responses or withdrawal from participation in the study. A debriefing statement for IRB review should be submitted along with the informed consent form.

The informed consent form (or electronic consent) signed by a study subject, or the subject's legally authorized representative, must be the version currently approved by the IRB that bears the date stamp of the IRB. One copy must be given to the subject and the original consent with the original signature must be maintained by the investigator. Another copy of the informed consent form must be maintained in the subject's research chart, medical record, or equivalent file in medical research studies.

### 10.10 Electronic Consent and / or Signatures

Electronic consents (eConsent) and electronic signatures may be used if the procedures for obtaining them, and the vendor, are approved by the IRB, and the risk of breach of confidentiality is minimized. The IRB will consider vendor security confidentiality issues - such as how a copy of the consent document may be provided for review if requested by the subject. Per FDA/OHRP guidance, "If properly obtained, an electronic signature can be considered 'original' for the purposes of recordkeeping." \*

## Chapter 10: Informed Consent Requirements

The subject must agree to use the electronic format and must be informed about their rights to obtain the electronic consent in non-electronic form and be provided description of any procedures that must be followed to withdraw their agreement to use an electronic record.

Vendors producing electronic consents will also need to comply with established FDA regulations. “Electronic” documents would be subject to a specialized set of requirements found at 21 CFR Part 11. Compliance with these standards is used to assure that electronic records are “trustworthy, reliable, and generally the equivalent to paper records and handwritten signatures executed on paper.” Investigators are responsible for ensuring compliance with 21 CFR Part 11. This regulation requires that the electronic system capture the record date that the subject or subject’s LAR provides consent.

The following consideration should be given when using eConsent technologies:

- The ability of individuals to access or use the technology, especially individuals with poor eye sight or impaired motor skills;
- The ability of the study team to verify the identity of the individual using the technology;
- the availability of the study team to answer questions of study participants; and
- Security measures to ensure the privacy and confidentiality of information collected with the electronic technology.
- All IRB-approved versions of an eConsent must be archived and easily retrievable. All procedures must be in compliance with FDA regulations for electronic records (Part 11, Electronic Records; Electronic Signatures – Scope and Application:

<https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm>)

Amendments to an eConsent may be provided in an electronic or paper format. Either is acceptable to convey and transmit updated information to the subject. OPRS and FDA regulations permit the flexibility of using electronic and paper informed consent methods independently or in combination throughout the course of the study.

For studies that involve social media websites, investigators must ensure informed consent language does not conflict with terms of service agreements from those websites (such as Facebook, Twitter).

### 10.11 Use of the Short Form

Use of [short form consent](#) is an option for any kind of research. Regulations do not limit the use of short form consent to translations only.

If informed consent is obtained using the Short Form method (oral translation of the consent form in a language understood by the participant supplemented with the written Short Form in the participant's language), the subject, or the subject's legally authorized representative, and a witness must sign and date the informed consent. If applicable, the subject or (legally authorized representative) must also sign the California Bill of Rights translated into a language understood by the subject. Refer to "[Translation of Consent Forms into Languages Other than English](#)" for additional information regarding use of the Short Form.

### Obtaining Consent from Non-English Speaking Subjects

When an investigator anticipates enrollment of non-English speaking subjects, the IRB-approved informed consent form must be translated into each anticipated language. When a study includes unanticipated non-English-speaking subjects, the investigator must provide short form consent to the subject or legally authorized representative (LAR).

### Guidelines for the Use of the Short Form

If there is occasional and unexpected need to enroll subjects who are not fluent in English, a written *short form* informed consent must be used in conjunction with the written IRB-approved English version of the consent. The *short form* consent includes the basic and possible additional elements of disclosure. The short form is available in English and many languages on the [OPRS](#) websites. Investigators can download the short form and fill in the blanks as appropriate. The language has already been approved by the IRB.

The process for enrolling subjects with the short form is outlined below. Substitute "Legally Authorized Representative (LAR)" for "subject" when an LAR is involved in the process. All of the following requirements must be completed:

- A translator must orally translate the entire IRB-approved English version of the consent form to the subject in a language understandable to him/her, and the

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subject must be given a copy of the translated "short form" consent document to read

- The entire consent process must include a witness to the oral presentation
- The IRB-approved English version of the consent form must be signed by the individual authorized by the IRB to obtain consent, and signed by the witness to the consent process. The translated short form must be signed by the subject and the witness to the consent process
- The California Bill of Rights must be provided to the subject for studies that involve a “medical experiment” as defined by California law. The Bill of Rights is available in the same languages as the short form. The subject must sign and date the form, AND
- The subject must be given copies of the IRB-approved English version of the consent form and the translated versions of the short form consent document and California Bill of Rights. The original signed English version with the original signed short form attached should be placed in the subject's research record, medical record, or equivalent file as appropriate.

### Translation of Consent Forms into Languages Other than English

When the study subject population includes people, who do not understand English, and the investigator or the IRB anticipates that consent interviews are likely to be conducted in a language other than English, the IRB will require translation of the IRB-approved consent documents into those languages.

#### Translation Options

If the study population is likely to include subjects whose primary language is Spanish, the consent documents must be translated into Spanish. When applicable, an electronic Spanish translated version of the informed consent should be requested from the Sponsor. The USC IRB will append USC-specific translated text to the sponsor form without altering format. The USC IRB will offer Spanish translation services to serve demonstrated needs on investigator initiated clinical trials. Details are available at the following link: [https://oprs.usc.edu/policies-and-procedures/consent\\_changes/](https://oprs.usc.edu/policies-and-procedures/consent_changes/). For investigator initiated, non-industry clinical trials, the USC IRB requires that the first

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Spanish-speaking participant be consented with the use of the [short form](#). Then, request a full consent translation into Spanish by contacting the IRB Analyst assigned to the study in iStar. More information can be found at: [Consent and Short Forms: Who Must Sign?](#)

For languages other than Spanish, it is the responsibility of the investigator or study sponsor to provide translation using a translation service. The investigator must obtain IRB approval of the English version of the forms before providing them to the translator. A consent form translated by a translation service must be submitted to the IRB along with a certificate of translation. The translated consent form will be uploaded into the iStar application and stamped by the IRB. Investigators will receive email notification that the translated consent form is ready for use.

For OHRP and FDA guidelines on obtaining consent from subjects who do not speak English, refer to the links below.

### *Helpful Links:*

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- OHRP “Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English”:  
<http://www.hhs.gov/ohrp/policy/ic-non-e.html>
- FDA “A Guide to Informed Consent – Information Sheet”  
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm#nonenglish>

### **10.12 Consent Documentation when Subjects Cannot Read, Hear, or Sign Consent Forms**

Additional protections are needed for subjects who cannot see, hear, or speak or who cannot read or sign consent forms. The consent process must be conducted in a language or manner understandable to the subject and must allow the subject to communicate his or her willingness to participate. The study team must ensure that the subject is adequately informed and properly document the consent process.

English-speaking subjects who cannot see or are unable to read and write may have the informed consent form read to them. A witness must be present during the consent process and must sign the consent form. Subjects who are unable to sign the consent form

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can consent to participate in the research by "making their mark" (providing an alternative form of signature) on the signature line. The name of the subject, date, and time (if applicable) can be completed for the subject by either the witness or the person obtaining consent. A note must be included in the research record stating the method used for communicating with the subject and the means by which the subject communicated agreement.

For non-English speaking subjects who cannot see, read, or write, the process described above should be used. The study team must use a consent form or short form translated into a language the subject understands.

People who can read but cannot physically write can give verbal consent. A witness must be present during the consent process and must sign the consent form. The name of the subject, date, and time (if applicable) can be completed for the subject by either the witness or the person obtaining consent. A note must be included in the research record stating the method used for communicating with the subject and the means by which the subject communicated agreement.

For people who can read and write but cannot hear or speak, sign language or specialized oral interpreters should be used to enhance communication with the study team. A witness must be present during the consent process and must sign the consent form. A note must be included in the research record stating the method used for communicating with the subject and the means by which the subject communicated agreement.

When consent is obtained from a Legally Authorized Representative (LAR), follow the procedures above substituting LAR for subject as applicable.

### 10.13 Waivers of Informed Consent

#### Waiver of Requirements of Informed Consent

In some situations, the IRB may waive the requirement for obtaining a signed informed consent [45 CFR 46.117\(c\)](#). Investigators may request the IRB waive some or all of the requirement for informed consent. The following describe the requirement for the approval of waiver.

### Non-exempt Research

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- a) The research involves no more than minimal risk to the subjects;
- b) The research could not practicably be carried out without the requested waiver or alteration;
- c) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- d) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- e) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

### FDA-Regulated Research

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA does not object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described above.



### *IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects (July 24, 2017)*

#### **Exempt and Flexed Research**

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- a) The research involves no more than minimal risk to the subjects; and
- b) The waiver or alteration will not adversely affect the rights and welfare of the subjects

#### **Exempt and Flexed Research**

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- c) The research involves no more than minimal risk to the subjects;
- d) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- e) If the research involves obtaining or retaining identifiable private information or identifiable biospecimens, the research could not practicably be carried out without retaining such information or biospecimens in an identifiable format

### **Waiver of Documentation of Informed Consent**

#### **Non-Exempt Research**

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds that the:

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- a) Only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality;

**Note 1:** Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)

**Note 2:** In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research is not FDA-regulated.

- b) The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers; or

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

### **Exempt and Flexed Research**

There is no IRB-related requirement for the researcher to obtain signed consent forms from participants. However, other laws or regulations, such as FERPA, may require that a signature be obtained.

### **Waiver for Public Benefit and Service Programs**

The IRB may waive informed consent requirements or the need to obtain informed consent for research for research involve public benefit and service programs that require approval by state or local officials ([45 CFR 46.116\(c\)](#))

### 10.14 Child Assent Special Requirements

Special informed consent procedures and forms are required when children participate in research. Children have not attained the legal age to consent to research treatments or procedures. Assent is a child's affirmative agreement to participate in research. Investigators must obtain permission from parents and agreement (assent) from children. Additional information about research involving children is found in [Section 14.1 – Protection of Children Involved as Subjects in Research](#).

#### Requirements for Parental Consent

Subpart D of the federal regulations ([45 CFR 46 Subpart D](#)) addresses permissible research with children and consent requirements. Some situations require permission from one parent, while other situations require permission from both parents. In other cases, waiving the requirement to obtain consent may be necessary (See [Section 14.1 – Protection of Children Involved as Subjects in Research](#) for more about Subpart D).

##### Permission of One Parent

The IRB may find that the permission of one parent is sufficient for research to be conducted under [§46.404](#) (research not involving greater than minimal risk) or [§46.405](#) (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects).

##### Permission of Both Parents

Where research is covered by [§46.406](#) (referring to research involving greater than minimal risk and no prospect of direct benefit) and [§46.407](#), (specific requirements of IRB members to ensure the safeguard of vulnerable subjects), permission is to be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

##### Waiver of Consent Requirements

If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent

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requirements in [45 CFR 46 Subpart A](#) and [45 CFR 46.408\(b\)](#), provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law.

Additionally, Public Demonstration Projects may obtain a waiver of parental permission if the IRB finds that all criteria below are satisfied:

- The research is to be conducted by or subject to the approval of state or local government officials, and
- The research is designed to study, evaluate or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs, and
- The research could not practicably be carried out without the waiver or alteration, and
- The research is not FDA-regulated.

### **10.15 Providing Significant New Information / Findings (SNIF) to Participants**

Regulations require that participants be provided with significant new information/findings (SNIF) developed during the course of the research that may affect their willingness to continue participating [45 CFR 46.116(b)(5) and 21CFR50.25(b)(5)].

Examples of situations that may require the investigator to provide new information to the participants:

- Changes to the procedures
- Identification of new risks or that risks previously described are known to occur with greater frequency or severity than previously reported
- New investigator conflict of interest
- Notification of significant findings from related studies

### **Providing Significant New Information/Findings (SNIF) to Participants**

The IRB must review the new findings and approve the proposed method of informing participants. Changes in approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to participants [[21 CFR 56.108\(a\)\(4\)](#)].

### **Providing Significant New Information Involving an Apparent Immediate Hazard**

If an apparent, immediate hazard to participants is identified, participants must be notified and corrective actions implemented as soon as possible. The IRB must be informed and the investigator must submit a Reportable Event in iStar “Protocol Change Initiated to Eliminate Immediate Hazard” to the IRB [promptly](#) (within 10 days). (Please see “[Investigator Reporting of Internal Adverse Events to the USC IRB](#)”). Subsequently, an amendment with revised study documents (such as an updated consent form and updated protocol) must be submitted to the IRB within 30 days. The Principal Investigator must notify the sponsor as required by the sponsor or FDA.

When investigators must contact participants immediately, notification can be made in writing or verbally. However, study files must document when participants were notified, how they were notified (in person, by phone, or by email or letter), what information was provided to them, and who contacted them.

### **Significant New Information that Does Not Involve an Apparent Immediate Hazard**

If significant new information/findings do not warrant immediate notification of participants, the investigator must inform participants of the new information/findings using a consent document. The consent document requires prior IRB review and approval. The study participant will be asked to sign a new informed consent form that will include the significant new information. This will document the participant’s decision to remain in the study (“re-consent”).

### 10.16 Obtaining Consent for Screening Procedures

Screening procedures to determine eligibility are considered part of the subject selection and recruitment process, and therefore, require IRB oversight. Examples include collecting data directly from subjects through written screening tools, oral responses to questionnaires, accessing private information, and medical testing. Interactions or interventions performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. However, a partial waiver of HIPAA authorization for screening and recruitment is required to access medical records.

Depending on the nature of the research, consent may be required before any screening procedures are performed. There are several potential options for obtaining consent for screening procedures.

Examples of screening procedures that can be performed without consent:

- When no data is kept and no medical or psychological intervention occurs
- When screening activities generally pertain to non-medical minimal risk research
- When screening involves a procedure for which written consent is normally NOT required outside the research context

Screening procedures that require a separate consent form for screening:

- When requested by sponsor / IRB
- When screening involves a medical/psychological interaction or intervention that is greater than minimal risk or involves a procedure for which written consent is normally required
- When screening data are kept
- When impractical or not feasible to enroll a subject immediately after screening

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# Chapter 11

## Privacy, Confidentiality and HIPAA

This chapter describes the importance of privacy and confidentiality protections as required by [45 CFR 46.111](#), Food and Drug Administration (FDA) regulations [21 CFR 56.111](#), the Health Insurance Portability and Accountability Act (HIPAA, also known as the Privacy Rule), and state and local laws. The IRBs review each study to ensure that privacy of subjects and confidentiality of data are adequately addressed.

### 11.1 Privacy and Confidentiality

Privacy is about people. It refers to research participants' willingness to allow access to themselves and their information. Consideration of privacy includes the time and setting where private information is given, the nature of the information given, and who receives and uses the information.

Confidentiality is about data. It refers to the handling of information that a person has disclosed in a relationship of trust, with the expectation that it will not be divulged to others without permission.

IRBs must consider the protection of privacy and confidentiality as part of their ethical and regulatory duty to protect the rights and welfare of human subjects. Maintaining privacy and confidentiality helps to protect subjects from potential harms that could occur with a breach of confidentiality, such as psychological distress, loss of insurance, loss of employment, or damage to social standing. Often, particularly in behavioral research, the main risk to subjects is the possibility of a breach of privacy or confidentiality. The IRB must consider privacy and confidentiality for the entire duration of the study. The IRB must also consider confidentiality of research data after the study is finished.

Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information, except as required by law or released with the written permission of the subject. Subjects, including children, have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and to be assured that the confidentiality of their information will be maintained. The more sensitive the data, the greater the care investigators must take in obtaining, handling, and storing data.



During the consent process, investigators must explain what information will be collected, how it will be used, who will have access to it, and what will happen to it after the study ends. When applicable, investigators should explain any special precautions they will take to ensure confidentiality of sensitive information. This will allow subjects to understand how their information will be used and decide if potential confidentiality risks are acceptable to them.

### Research Data Security

The purpose of this policy is to establish data security requirements for the use, storage, sharing, transmission and destruction of information obtained about participants in USC human subjects research studies.

This policy applies to all human subject research data collected by or under the auspices of University of Southern California (USC) by faculty, students, post-doctoral scholars, affiliated investigators or other investigators using USC resources. This policy applies to data that may be (or has been) collected or stored in any form including, but not limited to electronic records, paper, and audio or video recordings. This policy applies to data stored within university owned equipment, privately owned equipment, internet services or that reside on removable electronic media (e.g. USB thumb drives).

Additionally, adherence to all USC-wide policies for research data is required (see policy for [Information Security](#) and the policy for [Protection of Social Security Numbers and Other Restricted Information](#)). Questions about complying with the Human Subjects Research Data Security policy should be directed to ITS Security.

Note: The European Union's General Data Protection Regulation (GDPR) regulates the use, access, collection, and processing of all personal data from the European Union, regardless of the citizenship or residency status of the individual to whom the data pertains. USC investigators conducting research with data from the EU should become familiar with their responsibilities established by the GDPR.

Investigators are responsible for implementing appropriate protections for sensitive data including identifying risks and impact of potential breaches. The IRB will verify the adequacy of the protections. If the data is highly sensitive or used advance technology that exceeds the IRB expertise, then the IRB will seek a data security consultant in the relevant school/department.

Research data-sensitivity levels (de-identified, medium sensitivity, and highly sensitive) are defined in section V.

### **I. Protecting Medium/Highly Sensitive Data**

- Use University designated data centers or university approved cloud service providers
- Perform weekly vulnerability scans on systems and remediate any critical or high rated vulnerability
- Employ intrusion detection or review logs regularly
- Use up-to-date software
- Employ anti-virus/anti-malware software and update regularly
- Backup data on separate media to ensure recoverability
- Collect the minimum identifiable data
- Ensure any vendors or third parties handling data, including online services such as cloud storage providers, have a current, approved HIPAA Business Associate Agreement
- Whenever possible, de-identify and/or separate data elements into a coded data set and an identity-only data set.
- Limit access to personally identifiable information using the principle of strict need-to-know.
- Encrypt data if identifiable information is: (1) stored on a networked computer or device, (2) stored on or transmitted via the web, (3) stored on a computer or removable medium which is not permanently located in a secure location.
- Contact the IT administrators from the local school/unit as questions arise prior to IRB submission.

### **II. Requirements for Data Transmission, Sharing and Storage**

#### **Data Transmission and Sharing**

Highly sensitive data such as protected health information of research participants should not be housed on portable electronic devices. If portable electronic devices must be used, they should be encrypted to safeguard data and information. These devices include laptops, CDs, disc drives, flash drives, etc. Investigators and institutions also should limit access to highly sensitive data through proper access controls such as password protection and other means. Sensitive data should be transmitted only when the recipient has assured in writing that they will house the data in a secure storage system.

For storage of any data outside of USC/ USC networks, an agreement should be established that addresses the following questions:

- What security controls are in place to prevent the inadvertent or malicious disclosure of the data?
- What happens if a subpoena is issued?
- Does the recipient have Information Security/Cyber Liability insurance?

### **Data Storage**

Research data and materials related to human subjects research must be maintained and stored in a manner that complies with all applicable IRB and University requirements, and with any relevant contracts, data use agreements and federal regulations. Principal Investigators and other University faculty and staff who lead or administer research projects are responsible for recording, retaining, accessing, and storing their research records, and for communicating such systems and to the members of their research teams and to the IRB.

#### **Storing data on-campus**

Storage of medium or high-risk data on campus must comply with the USC policy for [Protection of Social Security Numbers and Other Restricted Information](#).

#### **Storing data off-campus**

Storing data off-campus with a third-party vendor must meet all the policies for data stored on-campus and must be stipulated in a contract with the vendor.

#### **Storage under a Data Use Agreement**

When data is shared using a Data Use Agreement, the agreement must state the terms of storage, destruction or return of the data during or after its use.

### **III. Establishing A Data Use Agreement**

A data use agreement (DUA) is an agreement that is required under the HIPAA Privacy Rule and must be entered into before there is any use or disclosure of a limited data set (defined below) to an outside institution or party. A limited data set is defined by HIPAA as protected health information (PHI). Covered entities must enter into a data use agreement with any recipient of a limited data set.

At a minimum, any DUA must contain provisions that address the following:

- Establish the permitted uses and disclosures of the limited data set;
- Identify who may use or receive the information;

- Prohibit the recipient from using or further disclosing the information, except as permitted by the agreement or as otherwise permitted by law
- Storage, destruction or return of the data during after its use
- Require the recipient to use appropriate safeguards to prevent an unauthorized use or disclosure not contemplated by the agreement;
- Require the recipient to report to the covered entity any use or disclosure to which it becomes aware;
- Require the recipients to ensure that any agents (including any subcontractors) to whom it discloses the information will agree to the same restrictions as provided in the agreement; and
- Prohibit the recipient from identifying the information or contacting the individuals.

### IV. Definitions

- **Anonymous data:** Data that has no code that can be traced back to an individual. IP addresses are identifiable even though the address is linked to the computer and not specifically to the individual.
- **De-Identified:** The identity of the subject cannot be readily ascertained. Requires the removal of all 18 HIPAA identifiers including geographic information and elements of dates.
- **Coded:** a code (number, letter, symbol, or any combination) exists that links to the identity of the individual. A key exists, enabling linkage of the code to the identifying information.
- **PHI:** Protected Health Information any identifiable health information used or created for healthcare or research, relating to the individual's past, present or future physical or mental health condition or payment for health care.
- **PII:** Personally Identifiable Information: “(1) any information that can be used to distinguish or trace an individual's identity, such as name, social security number, date and place of birth, mother's maiden name, or biometric records; and (2) any other information that is linked or linkable to an individual, such as medical, educational, financial, and employment information.”
- **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is

## Chapter 11: Privacy, Confidentiality and HIPAA

taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).

- **Individually Identifiable:** private information or specimens that can be linked to specific individuals by the investigator(s) either directly or indirectly.

## V. Levels of Research Data Sensitivity Chart

Risk Category	Description of data/ technology used	Examples
<b>De-identified and non-confidential information</b>	De-identified research information about people and identifiable information which, if disclosed, possesses no risk of harm to subjects.	<ul style="list-style-type: none"> <li>Public records</li> <li>De-identified sensitive information</li> </ul>
<b>Medium Sensitivity</b>	<p>Individually identifiable information for which confidentiality protections have been assured by the principle investigator.</p> <p>A limited data set excludes <u>all</u> of the following direct identifiers:</p> <ul style="list-style-type: none"> <li>Names</li> <li>Street addresses (other than town, city, state, and zip code)</li> <li>Telephone and fax numbers</li> <li>Email addresses</li> <li>Social security numbers</li> <li>Medical record numbers</li> <li>Health plan beneficiary numbers</li> <li>Account numbers</li> <li>Certificate/driver's license numbers</li> <li>Vehicle identifiers and serial numbers, including license plate numbers</li> <li>Device identifiers and serial numbers</li> <li>URLs and IP addresses</li> <li>Biometric identifiers</li> <li>Full face photographic images and any comparable images</li> </ul>	<ul style="list-style-type: none"> <li>Dates, such as admission, discharge, service, and date of birth (DOB)</li> <li>City, state, and zip code (not street address)</li> <li>Any other unique code or identifier that is not listed as a direct identifier.</li> </ul>
<b>High Sensitivity (Extremely sensitive individually identifiable information)</b>	<p>Information that could cause harm to an individual if disclosed, including risk of criminal liability, psychological harm or injury, employability, or social harm that is linked to the identifiers below:</p> <ul style="list-style-type: none"> <li>Names</li> <li>Geographic subdivisions smaller than a state</li> <li>Dates (except year only) directly related to an individual, including birth date, date of death, admission date, discharge date; and all ages over 89 (except ages may be aggregated into a single category of age 90 or older)</li> <li>Telephone and faxes numbers</li> <li>Email addresses</li> <li>Social security numbers (SSN)</li> <li>medical record numbers (MRN)</li> <li>Health plan beneficiary numbers</li> <li>Account numbers</li> <li>Certificate/driver's license numbers</li> <li>Vehicle identifiers and serial numbers, including license plate numbers</li> <li>Device identifiers and serial numbers</li> <li>Web Universal Resource Locators (URL)</li> <li>Internet Protocol (IP) addresses</li> <li>Biometric identifiers (including finger and voice prints)</li> <li>Full face photographic images and any comparable images</li> <li>Any unique identifying number, characteristic or code</li> </ul>	<ul style="list-style-type: none"> <li>Protected Health Information subject to HIPAA.</li> <li>Student record information protected by FERPA.</li> <li>Information subject to the Payment Card Industry Data Security Standard (PCI DSS)</li> <li>In California, compromised information triggers breach notification requirements of California Trigger Notice. Breach notification laws define the categories of "trigger information". <a href="https://oag.ca.gov/ecrime/databreach/reporting">https://oag.ca.gov/ecrime/databreach/reporting</a></li> <li>Criminal justice records</li> </ul>

### Helpful Links:

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- [USC Information Technology Services / Data Storage](#)
- [Information Security](#)
- [Protection of Social Security Numbers and Other Restricted Information](#)

### Types of Identifiable Information

Information through which subjects may be identified include names, student identification numbers, hospital ID numbers, social security numbers, driver's license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth-grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards (described below) should be provided to ensure confidentiality.

### Guidelines for Protecting Confidentiality

- Limit recording of personal information to that which is absolutely essential to the research
- Store personally identifiable data securely and limit access to the Principal Investigator (PI) and authorized staff
- Code data as early in the research process as possible, and plan for the ultimate disposition of the code linking the data to individual subjects
- Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. If a [Certificate of Confidentiality](#) is requested for a study, the consent must include specific language. See the IRB Informed Consent Template and Instructions. For more information about Certificates of Confidentiality, refer to: <https://humansubjects.nih.gov/coc/index>
- Do not disclose personally identifiable data to anyone other than the research staff without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).

## Chapter 11: Privacy, Confidentiality and HIPAA

Investigators must describe their plans for protecting privacy and confidentiality in the iStar application. The IRB evaluates the investigator's plans, including:

- The settings in which potential participants will be approached and research procedures will be performed
- The settings in which data will be recorded, reviewed, and stored
- The method for recording data and labeling samples (identifiable, coded, or anonymous)
- The amount and type of data collected (to ensure that only the minimum amount necessary is collected)
- The study staff who have access to data
- Security measures in place to prevent inappropriate access to and disclosure of data
- Release of data or samples to third parties
- Destruction or de-identification of data at the end of the study

The IRB must decide on a study-by-study basis whether there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. The IRB decision is based on the sensitivity of the information obtained in the research and the protections promised to participants.

The IRB Directors are authorized to sign Certificates of Confidentiality.

[Provost Signature Authorization 7-25-2016](#)

### 11.2 Limits to Privacy and Confidentiality

Depending on the subject matter of the research, there may be limits to the investigator's promise of confidentiality to the subject. An example would be if a subject reveals information about possible child or elder abuse or if the investigator and/or the research



staff discover the possibility of abuse. (See [Section 13.13 – Mandatory Reporting](#) for more information.) The informed consent form must explain any limits to confidentiality.

### **Mandated Reporting of Abuse**

California law requires reporting of abuse or neglect of the elderly, dependent adults, and children to law enforcement and/or protective services agencies. California law also requires reporting of some communicable diseases to public health agencies. California law defines who is a mandated reporter and what agencies receive reports in each of these situations. Mandated reporting limits the confidentiality that can be promised to research participants. As a researcher, mandated reporters who observe or suspect child/elder abusive or neglect must report the incident. Student researchers although not mandated reporters, must inform their faculty advisor of their concern. Additional information is found in [Section 13.13 – Mandatory Reporting](#).

Participants must be informed if the investigator is a mandated reporter. The informed consent form should disclose what types of information must be reported to outside agencies by the research staff.

USC policies and procedures covering “mandated reporter” and the reporting of abuse/neglect can be found at the following site: <http://policy.usc.edu/mandated-reporters/>. [Appendix A](#) of the above policy provides a list indicating who are considered mandated reporters.

### **Mandated Reporting of Positive Results of Communicable Disease Testing**

California law requires health care providers to report certain communicable diseases to local health authorities. For research that includes testing for HIV infection, hepatitis, tuberculosis, sexually transmitted diseases, and other communicable diseases, participants must be told that the investigator is a mandated reporter. The informed consent form should disclose what positive test results will be reported to public health agencies ([California Code of Regulations Title 17, Section 2500](#)).

### Sponsor Monitoring of Research Records

In signing the consent and HIPAA form, subjects authorize monitors and auditors from funding agencies, sponsors, and regulatory agencies to access participants' study files to verify study-related data. Investigators must ensure that only the data described in the protocol and the access agreed to by participants in the informed consent and HIPAA authorization forms is available to external monitors. Research personnel often keep "shadow" research files that contain copies of source documentation for the purpose of protecting a subject's entire record accessible to third parties. Investigators must exercise caution to confirm that the privacy or confidentiality promised in the iStar application/informed consent are met regardless of whether records are kept in electronic or paper systems.

### 11.3 State Laws Addressing Privacy and Confidentiality

IRBs must consider state laws concerning privacy and confidentiality when reviewing research. Federal regulations require the IRB to evaluate the acceptability of proposed research in terms of applicable law, which includes state law. Investigators must comply with state law regarding privacy and confidentiality.

### Research Related to HIV or AIDS

The [California Health and Safety Code \(Section 121075-121125\)](#) provides additional protections for confidential research records in studies relating to HIV or AIDS.

"Confidential research records" includes any data in a personally identifying form developed or acquired by any person in the course of conducting research relating to AIDS.

Confidential research records developed or acquired by any person in the course of conducting research, or a research study relating to AIDS, shall be confidential:

Confidential research records may be disclosed in accordance with the prior written consent of the research subject to whom the confidential research records relate. Any disclosure made pursuant to such prior written consent shall contain the following statement:

*This information has been disclosed to you from a confidential research record the confidentiality of which is protected by state law and any further disclosure of it without specific prior written consent of the person to whom it pertains is prohibited. Violation of these confidentiality guarantees may subject you to civil or criminal liabilities.*

Confidential research records may be disclosed without prior written consent of the research subject to whom the confidential research records relate in the following circumstances:

- To medical personnel to the extent it is necessary to meet a bona fide medical emergency of a research subject, and
- To the California Department of Health Services for the conduct of a special investigation of the sources of morbidity and mortality and the effects of localities, employments, conditions and circumstances on the public health and for other duties as may be required in procuring information for state and federal agencies regarding the effects of those conditions on the public health

The content of any confidential research record shall be disclosed to the research subject, the legal representative of the research subject if the research subject is a minor, or the personal representative of a deceased research subject to whom the record pertains within 30 days after a written request is made for such records by the research subject or the legal representative.

### **Hereditary Disorders**

The California Health and Safety Code ([Section 124980](#)) addresses confidentiality related to hereditary disorders such as sickle cell anemia, cystic fibrosis, and hemophilia.

All testing results and personal information obtained from any individual related to hereditary disorders, or from specimens from any individual related to hereditary disorders, shall be held confidential and be considered a confidential medical record except for information that the individual, parent, or guardian consents to be released, provided that the individual is first fully informed of the scope of the information requested to be released, of all of the risks, benefits, and purposes for the release, and of the identity of those to whom the information will be released or made available.

Prior consent for the release of such information is not required in the following situations:

- Data compiled without reference to the identity of any individual
- Data compiled for research purposes, so long as the research has been reviewed and approved by an IRB, who must certify its approval of the research to the custodian of the information and further must certify that in its judgment the information is of such potentially substantial public health value that modification of the requirement for legally effective prior informed consent of the individual is ethically justifiable.

NOTE: USC legal opinion interprets this statute to indicate that as long as the IRB certifies that the research is approved and that the information is of a potentially substantial public health benefit, prior consent by the subject need not be obtained in order to obtain the records from the custodian. There is some concern, however, that this may conflict with the HIPAA Privacy Rules, which would require authorization by the subject for the release of his or her medical records, whether related to a hereditary disorder or not. For research where these issues arise, the IRB and/or the Office of Compliance will interpret on a case-by-case basis.

### 11.4 Certificate of Confidentiality

Certificates of Confidentiality (COCs) are documents issued by the National Institutes of Health (NIH) and other federal agencies (such as DOJ, FDA, CDC) to protect against forced disclosure of identifiable research information. They allow investigators and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. COCs may be granted for studies collecting sensitive information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. NIH will issue a COC for a study that fits the NIH mission regardless if the study has federal funding or not.

Examples of sensitive information that may require a COC include:

- Genetic susceptibility or family pedigree

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- Mental illness
- High risk sexual attitudes, preferences, and practices
- Substance abuse or other illegal behaviors
- Participation in exposure effects studies that later become litigious, such as breast implants or environmental or occupational exposures

By protecting investigators and Institutions from being compelled to disclose information that would identify research participants, COCs help the investigator achieve research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

The certificate states the date it becomes effective and the date it expires. A COC protects all information identifiable to any individual research participant during the time certificate is in effect. If the research extends beyond the expiration date, an extension of coverage must be requested. However, **the protection afforded by the certificate is permanent**. All personally identifiable information obtained about subjects in the project while the certificate is in effect is protected in perpetuity.

While certificates protect against **involuntary** disclosure, research subjects might voluntarily disclose their own information or authorize (in writing) the investigator to release information to others. In such cases, researchers may not use the certificate to refuse disclosure. Researchers must still comply with mandatory state and local reporting of child or elder abuse, reportable communicable diseases, or a subject's threatened violence to self or others. Additionally, the certificate does not prevent audits of the study by federal agencies such as the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP).

The informed consent form must explain that a COC has been obtained for the study. The consent form should explain the protections it affords as well as the limitations of protection. The IRB template informed consent forms contain language that should appear when a COC is obtained.

The IRB understands there is a slight risk that data may be subpoenaed before the certificate is received and would not be protected by the certificate. In these cases, the USC IRB will decide if the risk outweighs the benefit of proceeding with participant recruitment and data collection before the certificate was granted. Data collected before

the certificate is granted are protected by the certificate once it is granted so the risk pertains only to the period of time between data collection and receipt of the certificate

### How to Obtain a Certificate of Confidentiality

Investigators may choose to apply for a COC, or the IRB may require that an investigator obtain one. The following steps are required to request a COC:

- Investigator indicates in the IRB application that a COC will be requested for the study
- Investigator completes a COC application and drafts and signs a cover letter to be additionally signed by the designee.

Contact the IRB to obtain Institutional Official (IO)/IO designee signature.

- Investigator submits the application to NIH (or other agency) according to the agency's application procedures

IRB Study Approval\* Letter (may be included in IRB memo – item 1)

**\*IRB approval may be granted even though receipt of a COC is pending as long as the consent form(s) indicate the Principal Investigator has applied for a Certificate of Confidentiality from an HHS agency. Once received the PI must upload the certificate of confidentiality into iStar and submit an amendment to update the consent informing participants the data is covered under a COC.**

### Helpful Links

- DHHS Certificate of Confidentiality Kiosk:  
<http://grants.nih.gov/grants/policy/coc/index.htm>
- DHHS Frequently Asked Questions on Certificates of Confidentiality:  
<http://grants.nih.gov/grants/policy/coc/faqs.htm>
- DHHS Certificate of Confidentiality Contacts:  
<http://grants.nih.gov/grants/policy/coc/contacts.htm>

- OPRS Essential Elements for a Certificate of Confidentiality:  
<http://oprs.usc.edu/review/confident/>
- [Provost Signature Authorization 7/25/2016](#)

### 11.5 Health Insurance Portability and Accountability Act (HIPAA)

The federal HIPAA Privacy Rule went into effect April 14, 2003. The law generally prohibits health care entities such as health care providers, hospitals, nursing facilities, and clinics from using or disclosing protected health information without written authorization from the individual (HIPAA authorization). The Privacy Rule is in Title 45 of the Code of Federal Regulations, in Part 160 and in Subparts A and E of Part 164. More information about the Privacy Rule can be found at the Health Information Privacy site of the Office for Civil Rights (OCR) at: <http://www.hhs.gov/ocr/hipaa>.

#### Protected Health Information (PHI)

Protected health information (PHI) is any identifiable health information relating to the individual's past, present, or future physical or mental health condition, including payment for health care. When health information is individually identifiable and held by a “covered entity” it is likely to be PHI. A covered entity is a healthcare provider, healthcare clearinghouse, or health plan that transmits health information electronically. The HIPAA rule governs the use of individually-identifiable health information when it is PHI.

#### HIPAA and Research

HIPAA regulations apply to research that involves the use and/or creation of protected health information (PHI). Investigators who obtain, use or create PHI must comply with HIPAA requirements during all phases of the research, from the initial identification of potential participants to the storage of data after the research ends. Investigators must limit their use and disclosure of PHI to the minimum necessary to achieve the stated goals of the research.

HIPAA regulations identify 18 elements that could be used to identify an individual

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- Patient names
- Dates (except year) directly related to an individual (such as date of birth, death, hospital admission, and discharge)
- Patient postal addresses including city, state, and zip code
- Patient telephone numbers
- Patient fax numbers
- Patient e-mail addresses
- Patient social security numbers
- Patient medical record numbers
- Patient health plan ID numbers
- Account numbers
- Certificate/license numbers belonging to a patient
- Patient vehicle identifiers
- Device identifiers and/or device serial numbers specific to a particular patient
- URLs
- IP address numbers
- Biometric identifiers, including finger and voice prints, belonging to a patient
- Full face photos and other comparable images of a patient
- Any other unique patient-identifying characteristic or code

HIPAA requirements apply when investigators obtain information containing any of these identifiers from a covered entity. If investigators obtain the information directly from the participant or from sources other than a covered entity (such as a research laboratory), the information is not considered PHI and is not subject to HIPAA requirements.



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Additionally, creation of PHI may also require that investigators obtain an authorization from subjects.

- If a hospital lab, CLIA-certified lab, or any other facility that is HIPAA-covered is involved in the generation of the health information, HIPAA authorization from subjects **is required**.

Investigators can obtain and use PHI for research in the following situations:

- When participants sign a written HIPAA research authorization allowing access to their PHI

Research participants authorize use of their PHI by signing the “USC HIPAA Authorization to Use Health Information for Research” form. Participants sign the HIPAA authorization form at the same time they sign the informed consent. USC requires that the two forms be separate.

The HIPAA authorization form (in English and Spanish) and instructions for completing the form are available at: <http://oprs.usc.edu/hsirb/hsirb-forms>. This form is prepared by the USC Office of Compliance, and the form cannot be modified except as described in the instructions. If a sponsor wishes to change or add language in the form, the investigator must submit the proposed changes to the USC Office of Compliance for review and approval before the form can be used.

State and federal laws limit the disclosure of certain PHI, even with a HIPAA authorization. Under California law, a covered entity cannot release HIV test results to a researcher unless the participant gives specific permission. Release of information about mental health treatment also requires specific permission. Federal law limits the disclosure of information about alcohol and drug treatment from medical records unless the participant gives specific permission. Participants can give specific permission for these disclosures by initialing the applicable section of the USC HIPAA authorization form.

- When the IRB grants a waiver or alteration of HIPAA authorization, allowing PHI to be used in research without written authorization from participants

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Under HIPAA regulations, IRBs and Privacy Boards have the authority to grant a partial or full waiver of the requirement for written authorization by research participants. A partial waiver of HIPAA authorization allows investigators to use PHI to identify, screen, and recruit potential participants. A full waiver of HIPAA authorization allows investigators to use PHI for all study activities without getting authorization from participants. Investigators request full or partial HIPAA waivers when they complete the iStar application. Under the Privacy Rule (45 CFR 164.512(i)(1)(i)), the IRB can grant HIPAA waivers if the following criteria are met:

1. The use or disclosure of protected health information involves no more than minimal risk to the individuals or their privacy, based on:
  - a. An adequate plan to protect identifiers from improper use and disclosure,
  - b. An adequate plan to destroy the identifiers at the earliest opportunity (unless there is a health or research justification for retaining identifiers or such retention is otherwise required by law), and
  - c. Adequate assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research permitted under this policy
2. The research could not be practicably conducted without the alteration or waiver, and
3. The research could not be conducted without access to and use of the protected health information

If the HIPAA waiver is granted, the IRB correspondence to the investigator will document and explain the waiver.

- When the investigator obtains only de-identified health information

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HIPAA regulations allow a covered entity to use or disclose health information that has been de-identified. Health information that has been de-identified is not considered protected health information. De-identification involves removal of the 18 identifiers of the individual or the individual's relatives, employers, or household members (listed above). When investigators obtain only de-identified health information for research, HIPAA requirements do not apply; no written authorization or waiver is needed to conduct the research.

- When the investigator obtains a *limited data set* containing only selected identifiers

The Privacy Rule allows investigators to obtain and use a “limited data set” for research without authorization from the participant or a waiver of authorization. In a limited data set, 2 of the 18 HIPAA identifiers remain but the other 16 identifiers are removed. Limited data sets can include the following identifiers of participants and their relatives, household members, or employers:

- Dates (date of birth, date of death, and dates of service, such as hospital admission and discharge)
- Age
- City, state, and ZIP code

Investigators must sign a Data Use Agreement to obtain and use a limited data set. The Data Use Agreement is an agreement between the covered entity holding the PHI and the investigator who receives the limited data set. The agreement explains how the data will be used and protected and identifies the obligations of the investigator using the limited data set. The USC Data Use Agreement is available at: <http://policy.usc.edu/hipaa>.

- When the investigator obtains information about deceased individuals

The Privacy Rule protects identifiable health information after an individual dies. An investigator who wishes to obtain PHI of deceased people for research purposes can obtain the PHI only if certain conditions are met. The investigator must certify that the PHI is being sought solely for research on the PHI of decedents, that the PHI is necessary for the research, and that documentation of the death of each individual will be provided if requested by the covered entity. If these conditions are met, the PHI can be used without a written authorization or

waiver of authorization. Investigators must complete the form “[Researcher Request for Decedents’ Protected Health Information](#)” to obtain the PHI.

NOTE: HIPAA regulations have a “Preparatory to Research” provision that permits researchers to obtain and use PHI to prepare a research proposal. Under this provision, researchers are not allowed to remove PHI from the covered entity. Because Keck Hospital of USC and LAC+USC Medical Center are different covered entities, the preparatory to research provision is not practical for a study conducted at both sites. Investigators should request a partial waiver of HIPAA authorization for recruitment and screening.

### **Role of the USC IRBs Related to HIPAA**

The USC IRB acts as the Privacy Board for Keck Medicine of USC and LAC+USC Medical Center. In this capacity, the IRB will consider and make determinations about partial or full waivers of HIPAA authorization. The IRB reviews the HIPAA sections of the iStar application and advises investigators about HIPAA applicability and the need for written authorization. An IRB Chair, or other IRB member as designated by the Chair, may approve a waiver of HIPAA authorization for a research study that meets specific criteria. However, the Privacy Officer in the USC Office of Compliance is responsible for the content of HIPAA authorization forms. The USC Office of Compliance is also responsible for HIPAA training and oversight of HIPAA compliance at USC.

For more detailed information regarding HIPAA policies, forms, procedures, and training, please go to the Office of Compliance website: <http://ooc.usc.edu/health-information>. HIPAA authorization forms for non-research activities such as fundraising, marketing, and public relations are also available at this website.

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## Chapter 12

# Subject Compensation and Recruitment

Subject compensation and recruitment issues are significant concerns of the IRB. Compensation must not be excessive or coercive. Recruitment materials must reflect the true nature of the research and not mislead potential participants. This chapter explores these issues and discusses criteria for recruitment and subject compensation including industry sponsored studies.

### 12.1 Compensation

Compensation for participation in research remains a contentious issue with no regulatory guidelines. However, many papers have been written about subject compensation and guidelines have been suggested. Compensation takes many forms such as school supplies, gift certificates, parking reimbursements, meal coupons, nominal gifts, lotteries or cash.

The plan for compensating subjects must be submitted to the IRB in the study application. In addition, the form of compensation must be described in the informed consent document (such as cash, gift card, or chance to win a gift) as well as a description of the conditions under which a subject would receive partial or no payment.

For participation in an FDA regulated, sponsored trial, compensation may not be offered in the form of a discount coupon on the purchase price of the product after it has been approved for marketing.

#### Guidelines for Compensating Research Participants:

- Payment for participation in research should not be offered as a means of coercion. Rather, it should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Compensation may not be withheld contingent on the subject's completion of the study.
- In cases involving ongoing participation, compensation should be given on a reasonable, prompt, and prorated basis to avoid possible coercion. The payment should be made throughout the course of the study, contingent on participation as described in the protocol.

- The Principal Investigator and IRB should consider the risk, duration of participation, effort required, and local economy when determining appropriate compensation for a study population. Additional caution should be exercised when establishing compensation for greater than minimal risk studies. Economically disadvantaged subjects are especially vulnerable to undue influence from excessively high levels of compensation.
- It is acceptable to provide a chance to receive a gift as a form of compensation in lieu of providing cash or other remuneration. The “thank you” gift is commonly used by student investigators with limited funds. Examples of gifts include a chance to win a “thank you” item such as an MP3 player, cellular phone, or gift-card.

### **Compensation for U.S. Military Personnel for Department of Defense (DOD) Sponsored Research**

When Department of Defense-sponsored research is conducted on US military personnel, the following limitations on dual compensation for US military personnel apply:

- Prohibits an individual from receiving pay from more than one position for more than 40 hours of work in one calendar week.
- Includes temporary, part-time and intermittent appointments.

Being a research subject is generally not a part-time job nor is it an intermittent appointment. There are some situations where active duty can be compensated. The Army allows this when military personnel are 'off-duty' or on 'official leave'. If the research is greater than minimal risk the Commanding Officer must give permission for the military personnel to enroll. DOD allows compensation for military personnel up to \$50 per blood draws whether on or off duty.

## **12.2 Recruitment**

Recruitment of subjects is considered to be the beginning of the informed consent process. Recruitment is one of the most challenging aspects of research involving human subjects. Recruitment is often conducted by use of posters and brochures displayed in

## Chapter 12: Subject Compensation and Recruitment

public spaces that include hospitals, clinics and laboratories. Traditional radio and television announcements, along with websites and social media are also often used.

The pressure to enroll subjects raises ethical challenges for investigators and research staff. Recruitment of subjects must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition being studied. All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with FDA, OHRP, and HIPAA regulations, as applicable.

For additional information, refer to FDA Information Sheet [“Recruiting Study Subjects”](#).

### Recruitment Materials

When a project requires IRB review, all recruitment materials under local control including advertising and marketing materials must be reviewed as part of the study. Any recruitment materials generated by USC investigators or research personnel must be submitted to the IRB for review and approval before they can be used.

The following information should be included in recruitment materials:

- Accurate description of the research purpose
- Name and address of the investigator or facility (including university affiliation and/or department)
- Condition under study or purpose of the research
- Eligibility criteria
- Time commitments required
- Location of the research
- Person to contact for further information

The following information should NOT be used in recruitment materials:

- Coercive language
- Claims that a device or drug is safe and effective



## Chapter 12: Subject Compensation and Recruitment

- The words “new treatment,” “new medication,” or “new drug” if the test article is investigational
- Promises of “free medical treatment”
- Amount of payment, dollar signs, or the words “free” in large or bold face type
- Compensation should not be excessive relative to the nature of the project
- Statements or implications assuring favorable outcome or other benefits beyond what is outlined in the consent document and protocol
- Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device
- Exculpatory language

Note: content allowed in recruitment materials may differ between the University Park and Health Sciences Campuses. If you have questions, contact your local IRB for more information.

### **National Recruitment Materials Not Reviewed by the IRB**

Industry sponsors often produce recruitment materials that are used on a national basis and that cannot be modified by local sites. Examples include websites, radio or television advertisements, and call center scripts. Recruitment materials that cannot be modified by USC investigators will not be reviewed, approved, or acknowledged by the USC IRB. These materials should not be attached in the iStar application.

### **12.3 Payment for Referrals (Finder’s Fees) Are Not Permitted**

USC policy does not allow any finder’s fees. Investigators, or any other member of the research team, may not offer payment to subjects (prospective, previously enrolled, or currently enrolled) for referring their friends, family member, or other individuals. Finder’s fees may not be offered to other investigators, clinicians, researchers, or any other individual or group for referring potential subjects.

## Chapter 13: Investigator's Role and Responsibilities

### Chapter Contents

- 13.1 – Definition and Role of Principal Investigator (PI)
- 13.2 – Investigator-Initiated Research and Sponsor-Investigators
- 13.3 – Educational Requirements
- 13.4 – Professional Qualifications of PIs
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- 13.14 – Suicidal Ideation in Research
- 13.15 – Investigator and Staff Safety

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## Chapter 13

# Investigator's Role and Responsibilities

This chapter defines the role of Principal Investigator, co-investigator, and student investigator in human subjects research. Additionally, it identifies the specific responsibilities, qualifications, and interactions of an investigator

### 13.1 Definition and Role of Principal Investigator (PI)

The term Principal Investigator (PI) implies specific responsibilities and interactions for conducting research. Investigators have a responsibility to protect the rights and welfare of participants and following applicable federal, state, and local regulations.

Investigators are expected to follow ethical principles and standards appropriate for their discipline and research. Investigators must also follow Good Clinical Practice (GCP) guidelines in designing and conducting clinical trials. The PI bears ultimate responsibility for the scientific, technical, and administrative aspects of the research project, even when certain tasks have been delegated to or co-investigators, sub-investigators, staff, or students. USC policies, procedures, and education programs are provided to help investigators carry out research studies ethically. Refer to [Section 13.3 - Good Clinical Practice \(GCP\) Course](#) for training requirements.

### Who may be a Principal Investigator on an IRB application

At USC, the following may be listed as Principal Investigator in iStar:

- USC faculty and staff (excluding temporary personnel)
- “Students” may include undergraduates, master and doctoral students, medical students, residents/interns, clinical, research and postdoctoral fellows. Student investigators must designate a Faculty Advisor on the IRB application. Faculty Advisors are responsible for the scientific and ethical quality of student research projects. For more information, see [Section 13.7 – Faculty Advisor's Assurance for Student Investigators](#)

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- PIs who are not USC faculty must also adhere to USC Policy.

In contrast to who may be listed as a PI in iStar on an IRB application – for grants management, principal Investigators can only include:

Tenured, tenure track, and non-tenure track faculty, and research scientists (with the exception of lecturers, adjunct, and part-time clinical faculty). Postdoctoral, Research Associates and Postdoctoral Teaching Associates, as defined by USC's Postdoctoral Scholars Policy, may act as co-principal investigators on sponsored projects, but may not be principal investigators unless a specific waiver and approval is granted upon recommendation by the Department and approval of the appropriate Dean. The signature of the Dean/Department designee on a Proposal Approval Record (PAR) is equivalent to departmental authorization that the person may act as a principal investigator.

For additional information refer to the [Guide to Research at USC](#) and the [Postdoctoral Scholars Policy](#).

### IRB Review of Investigator Qualifications

One of the responsibilities of the IRB is to determine that the investigator is appropriately qualified to conduct and supervise the proposed research. In many cases, previous experience with an investigator allows the IRB to readily determine an investigator's qualification. However, if the IRB has no knowledge about an investigator, the IRB may request additional documentation to evaluate an investigator's qualifications (such as curriculum vitae, medical licensure or relevant publication). The IRB may also need to assess an investigator's training specific to the proposed study, particularly if the research involves higher risk, vulnerable subjects or novel technologies.

### Principal Investigator Responsibilities

The PI initiates the research proposal, defines the scope of the work, controls the conduct of research, and directly supervises any others (faculty, staff, or students) involved in the research. The PI is responsible for all expenditures under a grant (if applicable). The PI certifies the percentage of effort for other faculty and staff working on the project, certifies the accuracy of charges, notifies and communicates with sponsor personnel and collaborating organizations as needed, and manages the orderly execution and close out of the project.

### Investigator Responsibilities to IRB

PIs are responsible for ensuring that research is conducted according to valid research design and methods. PIs must adhere to an IRB approved study plan (protocol) and terms of the grant, contract and/or signed funding agreements as well as applicable laws, regulations, and institutional policies.

#### Initial Study Responsibilities

Prior to commencing research PIs must:

- Obtain approval from the appropriate department, institute and Dean or designee of the school for any proposal to be submitted to the IRB. Some schools (such as the Keck School of Medicine) require additional approvals, for example, from a Division Chief.
- Ensure appropriate research compliance committee approvals as deemed necessary. Studies may require school or department approvals as determined by the particular school or department, or other committees as deemed necessary.
- Submit an application for IRB review and approval. All IRB applications must be submitted through the iStar system.

**Note:** If research initiated at another Institution will be continued at that Institution and/or transferred to USC, the investigator must contact the USC IRB for information and submission requirements.

#### Ongoing Study Responsibilities

PIs must keep the IRB informed about their study and are required to:

- Submit annual progress reports when required by the IRB (see [Section 9.2 – Continuing Review](#))
- Submit an amendment to the IRB if a change to an IRB-approved study is necessary. The IRB must review and approve the changes before these are implemented unless the change to the study is initiated to prevent an immediate hazard to subjects (see [Section 9.1 – Amendments – Changes to Research after Approval](#))

- Submit reportable events and reports to the IRB as applicable. Reportable events and reports include adverse events, unanticipated problems involving risks to subjects, protocol deviations, data safety monitoring reports, and protocol changes initiated to eliminate immediate hazard to subjects (see [Section 7.15 – Reportable Events](#) and [Section 7.16 - Reports](#))

### **Close Out Study Responsibilities**

PIs must submit a final progress report to close out a study when a study is completed or terminated (see [Section 9.3 - Project Closure](#)). PIs who plan to leave USC and have active studies are required to:

- Close the study/ies: investigators must submit a final progress report (Continuing Review in iStar) or complete the “Close Study” activity in iStar
- Transfer the study to another USC investigator: submit an amendment to change the Principal Investigator
- Transfer the study to another Institution: investigators must close the study at USC by submitting a final progress report (Continuing Review in iStar) or complete the “Close Study” activity in iStar
- Continue study at USC and at another site: investigator should contact the USC IRB for more information and guidance.

## **13.2 Investigator-Initiated Research and Sponsor-Investigators**

Investigator-Initiated research has many different meanings. The National Institute of Health (NIH) uses the term “investigator-initiated research” to describe an investigator submitting an application to the NIH on a topic of his or her choice. Investigator-initiated research differs from targeted research in which investigators respond to an institute's call for applications in research topics specified in requests for applications (RFA) or requests for proposals (RFP).

Investigator-initiated research, in the context of clinical trials with an IND or IDE, is when an investigator is also considered the sponsor (sponsor-investigator) and must fulfill all regulatory requirements, FDA expectations, and monitoring expectations of a

sponsor. This differs from studies initiated and funded by a sponsor in which the sponsor provides the protocol. In addition to FDA regulations, sponsor-investigators must comply with California laws that affect research sponsors, such as manufacturing regulations for experimental drugs and devices. For additional information, refer to the [California Health and Safety Code Sections 111515-111545](#) and [111550-111610](#).

The iStar application requires investigators to indicate when the IND/IDE is held by USC faculty or investigator. Sponsor-investigators must also complete the Sponsor-Investigator attestation in iStar when submitting their study to the IRB. Investigators who plan to conduct sponsor-investigator research should contact the IRB Chair for assistance. For more information refer to [Section 18.4 – Sponsor-Investigators](#).

### 13.3 Educational Requirements

#### Human Subjects Protections Training

For an application to be approved by the USC IRBs, all study personnel must complete human subjects training. The online course used is provided by the Collaborative Institutional Training Initiative (CITI) at [www.citiprogram.org](http://www.citiprogram.org), providing a certificate of completion valid for three years.

Prior to a certificate expiring, a notification is sent from iStar to the researcher. Study personnel who have completed the human subjects basic course must renew their certification every three years. A refresher course is provided on [www.citiprogram.org](http://www.citiprogram.org).

Human subjects training is not required for studies that are considered Not Human Subjects Research (NHSR).

Proof of human subjects training from outside Institutions are accepted in lieu of CITI certification. For CITI educational requirements, refer to the OPRS website at: <http://oprs.usc.edu/citi>.

#### Good Clinical Practice (GCP) Course

Good Clinical Practice (GCP) represents the international ethical and scientific standard expected in design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.



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GCP training is required for all PIs and staff on studies meeting the NIH definition\* of clinical trials (as of 2015). GCP “refresher training”, [mandated in 2016](#) regulations, must be completed every three years after completion of the initial training. Sponsors of research may require additional GCP training.

GCP training is primarily intended for study staff who collect data through intervention or interaction with a subject, or have access to private identifiable information however, anyone on the study team may be asked to take it at the request of the IRB.

USC provides GCP online courses for initial and that refresher training through CITI. For more information, contact the OPRS at (213) 821-1154 or visit the OPRS website: <http://oprs.usc.edu/citi>.

*\*A clinical trial means a “research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes”. (46.102)*

### HIPAA Course

The "Privacy Rule" also known as the Health Insurance Portability and Accountability Act establishes minimum Federal standards for safeguarding the privacy of individual's identifiable health information. For more information, refer to [Section 11.5 – Health Insurance and Portability Accountability Act \(HIPAA\)](#).

USC researchers who use/access protected health information are required to complete USC's HIPAA online educational program. For detailed information regarding HIPAA policies, forms, procedures, and to access the online educational program, visit the Office of Compliance's website: <http://ooc.usc.edu/hipaa-privacy-regulations>.

### 13.4 Professional Qualifications of PIs

No person is allowed to perform medical procedures at USC without being properly credentialed /licensed and have the required hospital privileges. Persons with a foreign medical degree/license are not credentialed /licensed to perform medical procedures in California.

Credentialing for licensure is the responsibility of the Office of Compliance.

The IRB may require new PIs (first time submitters) to provide a copy of their curriculum vitae and medical license, and if necessary, additional supporting information to document that the investigator is qualified to conduct the research activity.

### **13.5 USC Investigators Conducting Multi-Site Research**

Procedures for USC Investigators conducting multi-site, research at non-USC sites or acting as the designated coordinating center are described below. This only applies to full board and expedited studies.

For additional information, refer to [Section 4.3 – Responsibilities Defined under the FWA](#).

The following procedures are for review and oversight of multi-site, non-exempt research.

#### **IRB Review of Resource Adequacy**

Once an investigator submits a new IRB application, it undergoes an administrative review by an IRB staff reviewer to ensure the application is complete. Upon initial review of the application, the staff reviewer ensures that the PI has listed any organizational units/departments/committees that are involved in the conduct of the research and that the investigator has secured approval from each department. If there are any organizational units that have not been listed, or the PI has not secured appropriate approval, the staff reviewer will send correspondence via iStar to the PI informing them that approval from the organizational units/departments/committee must be obtained prior to IRB approval.

Once a new study is submitted to the Full Board for review, it is the IRB committee's responsibility to ensure that the Investigator has listed the organizational units/departments/committees that are involved in and have secured their approval. If during the IRB's consideration of the study the investigator has not obtained approval, the IRB must stipulate that such approval be obtained prior to IRB approval. Additionally, the IRB considers whether resources are adequate to conduct proposed

research. For example, if the research involves specialized medical equipment or staff, the IRB may ask the investigator to confirm that such resources are available to conduct the research.

### **Non-USC / Non-Engaged Research Sites in Multi-Site Research**

USC investigators who conduct non-exempt research at non-USC sites are required to obtain permission to conduct the study when the site itself is not “engaged” (refer to [Section 4.2 – Engagement in Research](#)).

A permission letter is necessary to ensure that relevant information regarding the proposed research has been shared with, and agreed to, by the appropriate agency/institutional authority. The institutional authority is someone who has signatory authority (such as a Principal, clinic Director, school board Chair, or superintendent) for the organization. The site contact information in addition to the permission letter must be uploaded to the USC IRB application. A template letter is available on the IRB website: [Research Site Permission Template](#).

Waivers may be granted for minimal risk research and certain social behavioral studies.

#### Common Reasons for Waiving the Site Permission Requirement:

- Obtaining site permission is not practicable
- The research is being conducted at a large number of sites
- The data being collected is anonymous
- The behavior studied is not related to site/place
- The study involves less than minimal risk

#### Common Reasons for NOT Waiving the Site Permission Requirement:

- Research involves greater than minimal risk
- Safety concerns for participants or researchers
- Permission is required by the site (such as LAUSD, health clinics, hospitals)

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- Amount of time and effort required to obtain permission is minimal, and a courtesy
- Subjects are vulnerable and permission letters are usually required (children, cognitively impaired populations) (See [Chapter 14 – Vulnerable Subject Populations](#))

### **Multicenter Clinical Trials and Centralized IRB Review Process**

A centralized IRB review process involves an agreement under which multiple study sites in a multicenter trial rely in whole or in part on the review of an IRB other than the IRB affiliated with the research site.

Section 56.114 (21 CFR 56.114, Cooperative Research) provides that, “institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.”

### **NIH Single IRB (sIRB) for Multi-Site Research**

The National Institutes of Health (NIH) has mandated the use of a single IRB for multi-site research. The policy went into effect September 2017 for research funded by NIH with the purpose of streamlining the IRB process and easing administrative burden.

The NIH policy applies to grant applications received on or after January 25, 2018.

- [NIH Policy on the Use of a Single IRB \(sIRB\)](#)
- [Requisites for Single IRB](#)

HHS and NIH policies requires documentation in the form of an agreement which may be an MOU, Master Reliance Agreement, Authorization Agreement or similarly named.

### **USC as Coordinating Center for Multi-Site Research**

When USC is the coordinating center for a multi-site study, an adequate plan for the management of information from all sites relevant to the protection of participants is required. This plan should include:

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- A description of the types of events to be reported (such as unanticipated problems involving risks to subjects or others, adverse events, noncompliance, significant new information or findings, required protocol modifications)
  - When the reports must be made and sent to the coordinating center
  - How to make the reports to the coordinating center (specific forms, IRB forms)
  - To whom the reports should be made (such as lead investigator, other)
  - The process for disseminating these reports to the non-USC sites
- A description of how the coordinating center will ensure that each participating non-USC site has obtained IRB approval before initiating research activities

It is the Lead PI's responsibility to submit an adequate management and communication plan in iStar for research being conducted at multiple sites.

### **Data Coordinating or Statistical Center Responsibilities**

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This type of application places emphasis on how the Lead PI will assume responsibility for collection, storage, management and statistical analysis of data collected.

- Designing data forms
- Providing instruction on use of the forms
- Managing data and statistical analysis
- Overseeing secure data transmission and storage
- Protecting confidentiality of data and ensuring its integrity

### **Helpful inks**

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- OHRP: "Guidance on Engagement of Institutions in Human Subjects Research"  
<http://www.hhs.gov/ohrp/policy/engage08.html>
- Using a Centralized IRB Review Process in Multicenter Trials  
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm>

### 13.6 Investigator Conflict of Interest

The term “conflict of interest” in this policy refers to situations in which financial, or other personal considerations compromise, or have the appearance of compromising, an individual's professional judgments in proposing, conducting, supervising or reporting research. Conflicts of interest include non-financial as well as financial.

(See “[Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought](#)”)

**Conflicts of Interest may include but are not limited to the following:**

- Equity (stocks or options, do not include mutual funds)
- Recruitment incentives, bonus payments, (these are prohibited)
- Consulting Fees
- Speaking Fees
- Travel Reimbursement
- Gifts
- Corporate Officer or Board of Directors
- Other Employment Relationship
- Trademarks/Copyrights
- Licensing Agreements
- Royalty Payments
- Patent Holdings

Conflicts of interest must be declared in the IRB application when the study investigators, research personnel, or their immediate family/domestic partner have a financial interest, and/or intellectual property interest in the sponsor or products used with the project, **equal to or exceeding \$5,000 per year**. Investigators must also inform the IRB of relationships with the sponsor or party with economic interests in the research such as

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consultation agreements, speaker services or management roles. When these relationships exist, the potential conflict of interest is reviewed by the Office of Compliance.

HHS requires an annual disclosure for researchers who are proposing or have received HHS (including NIH, CDC, HRSA, and AHRQ) regardless of whether any of these interests give rise to a conflict of interest related to their research. The annual disclosure must be completed before a proposal can be submitted to HHS, and any identified conflicts must be managed before an account can be established. In addition, all HHS-funded investigators must complete training on conflicts of interest once every four years.

All potential or actual conflicts of interest must be disclosed online using the [diSClose](#) system.

The Conflict of Interest in Research Committee (CIRC) evaluates disclosed (or knowingly withheld) conflicts of interest.

### **For additional information regarding Conflict of Interest, refer to:**

- USC Office of Compliance website:  
<http://ooc.usc.edu/>
- USC Conflict of Interest in Research Policy:  
[http://policies.usc.edu/p4acad\\_stud/conflic\\_interest\\_research.html](http://policies.usc.edu/p4acad_stud/conflic_interest_research.html)
- USC Institutional Conflict of Interest Policy: <https://ooc.usc.edu/conflict-of-interest/institutional-conflict-of-interest-in-research/>
- USC Conflict of Interest in Professional and Business Practices:  
<https://ooc.usc.edu/conflict-of-interest/conflict-of-interest-in-professional-and-business-practices/>
- USC Relationships with Industry Policy:  
<http://ooc.usc.edu/relationships-industry>
- diSClose website:  
<https://disclose.usc.edu/>
- diSClose Training Videos:  
<http://ooc.usc.edu/diSClose-training-videos>

### 13.7 Faculty Advisor's Assurance for Student Investigators

When a student investigator is listed as the PI on the IRB application, a faculty member must also be listed as the faculty advisor. The faculty advisor electronically approves/signs-off on the IRB application to indicate they have reviewed the submission, it is ready for IRB review, and the faculty advisor assumes responsibility for oversight of the student's research.

The faculty advisor certifies that the student investigator is knowledgeable about IRB policies, and applicable federal regulations governing research with human subjects, and has sufficient training and experience to conduct the study in accordance with the approved protocol.

The Human Subjects Protection Program (HSPP) has implemented a mandatory human subjects education program (CITI) for all investigators, including students. Faculty advisors are considered key personnel and are required to complete CITI (see the IRB/OPRS websites for more information). Faculty advisors must ensure that student investigators and all other key personnel have completed the Human Subjects and the Health Insurance Portability and Accountability Act (HIPAA) Programs when required. The faculty member is also responsible for the scientific quality of the student research project submitted to the IRB.

### 13.8 Student Investigator's Assurance

A student investigator must electronically sign the IRB application. This means they agree to meet with their faculty sponsor on a regular basis to monitor study progress. If the faculty advisor is away, the student investigator will meet with the arranged alternate faculty advisor who will assume responsibilities.

The student investigator is expected to be familiar with the policies contained in USC's Federalwide Assurance(s). Prior to initiating research activities, student investigators must complete the Human Subjects Education Program ([CITI](#)).



### 13.9 Failure to Submit a Project for IRB Review

IRB approval must be obtained before conducting human subjects research, publishing or presenting the data. Undergraduate honors papers, Masters theses, and dissertations that are human subjects research require IRB review.

The IRB may not approve applications where an investigator circumvents IRB policies and procedures by collecting data as a “non-research” activity, and then subsequently applying for IRB approval to analyze the data as existing data. It is in the investigator's best interest to carefully consider the likelihood of the data being used for future research purposes, and err on the side of caution in seeking IRB approval prior to commencing the work. The IRB does not grant retroactive approval.

### 13.10 Scientific / Research Misconduct

The University of Southern California is committed to maintaining an environment that promotes high ethical standards in the conduct of research. The University does not tolerate misconduct in any aspect of research and will deal with misconduct associated with research forthrightly in accordance with academic due process, and with respect for practices commonly accepted within the scientific community.

Scientific misconduct is defined by the federal government as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

Human subjects review does not include evaluation of possible scientific misconduct. Other university committees make these determinations. If there is reason to believe scientific misconduct has occurred in a human subject research project, the IRB will report it to the appropriate official.

At USC, allegations of research misconduct, involving human subjects, are reported by the IRB to the Vice President of Research, the Executive Director of the Office for the Protection of Research Subjects (OPRS), and the Senior Associate Vice President of the Office of Compliance, and General Counsel Office for further action (scientific misconduct is not necessarily under the sole purview of the IRB).

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If a USC investigator does not conduct research responsibly, according to federal regulations or University policy, the investigator is subject to both federal and USC consequences. USC is committed to fairly and uniformly investigating and reporting all instances of alleged or apparent misconduct involving research by members of the University community, regardless of the funding source. For information on how these issues are handled by the University, refer to the USC “[Policy on Scientific Misconduct](#).”

The *Responsible Conduct of Research* section of the HSPP websites contains links to information on the responsible conduct of research and tutorials on how to conduct research responsibly and ethically [<http://oprs.usc.edu/education/rcr/>].

### Helpful Links:

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- ORI Federal Research Misconduct Policy  
<https://ori.hhs.gov/federal-research-misconduct-policy>
- NSF Research Misconduct Policy  
<http://www.nsf.gov/pubs/2002/nsf02151/gpm9.jsp#930>
- NIH Research Misconduct Policy  
[http://grants.nih.gov/grants/research\\_integrity/research\\_misconduct.htm](http://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
- DHHS Public Health Service Policies on Research Misconduct  
<http://edocket.access.gpo.gov/2005/pdf/05-9643.pdf>

### 13.11 Adequate Funds and Ancillary Approvals

The investigator is required to document that adequate resources have been allocated for the research. In addition, the department head must indicate that the submission has been reviewed to assure that the investigator has the necessary knowledge and privileges to perform the study, and that sufficient resources and adequate funds are available to perform the study as described in the submission. The IRB may not grant approval of the research until this documentation is complete.

It is the investigator's responsibility to identify all departments and organizational units that will be involved in the conduct of the research. The IRB may require ancillary

approvals in addition to those identified by the investigator. Ancillary approvals are authorizations from units/departments/committees whose services are critical to implementation of the research.

### 13.12 Intent to Publish Expectations

All investigators who intend to publish in an International Committee of Medical Journal Editors (ICMJE) journal must register their study in [clinicaltrials.gov](https://clinicaltrials.gov), regardless of whether it is a clinical trial or social behavioral study. The registration requirement applies to “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”

Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.”

The FDA / NIH and CMS (Center for Medicare and Medicaid Services) require study registration for all “[applicable clinical trials](#)”.

You must register in [clinicaltrials.gov](https://clinicaltrials.gov) before study begins. All researchers doing health outcome studies must register in [clinicaltrials.gov](https://clinicaltrials.gov). For additional information about study registration for clinical trials, refer to [Section 18.12 – Registration of Clinical Trials and Other Types of Research](#).

#### ***Helpful Links:***

- Memorandum from USC Vice President of Research “ICMJE Journals Require Advanced Registration of Human Studies”  
[https://oprs.usc.edu/files/2017/04/Registration-of-Human-Studies\\_4-7-14.pdf](https://oprs.usc.edu/files/2017/04/Registration-of-Human-Studies_4-7-14.pdf)
- List of Journals Following the ICMJE Recommendations  
<http://www.icmje.org/journals-following-the-icmje-recommendations/>
- OPRS webpage “Intend to Publish your Human Subjects Research Findings?”  
<http://oprs.usc.edu/review/publication/>

### 13.13 Mandatory Reporting

Mandated reporters are individuals who are obligated by law to report suspected cases of child and/or elder abuse and neglect. In general, any person who has contact with children or the elderly in a professional capacity is a mandated reporter, although laws vary from state to state, as does the legal entity to which reports must be made. USC policies and procedures covering mandated reporters and the reporting of abuse/neglect can be found at the following site: <http://policy.usc.edu/mandated-reporters/>. [Appendix A](#) of the above policy provides a list indicating who are considered mandated reporters. See also USC policy on Protecting Minors at: <https://policy.usc.edu/protecting-minors/>.

For the California Penal Code definition of mandated reporter see [Elder Abuse and Dependent Adult Civil Protection Act Section 15630 \(a\)](#) and [Child Abuse and Neglect Reporting Act Section 11165.7](#).

### Abuse Disclosure Notification in Consent Documents

Disclosing the obligation to report certain types of neglect and abuse in the informed consent process is only required for research projects involving mandated reporters. However, even though the requirement to report only applies to mandated reporters, [Section 11166.05](#) broadens the scope of possible reporting beyond the mandated areas by allowing (not requiring) mandated reporters to make reports regarding children suffering from “serious emotional damage or... at a substantial risk of suffering serious emotional damage, evidenced by states of being or behavior, including, but not limited to, severe anxiety, depression, withdrawal, or untoward aggressive behavior toward self or others”. This should be addressed in the informed consent process.

### Reporting of Positive Results of Communicable Disease Testing

Any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions (link to [Title 17, Section 2500](#)) may make such a report to the local health officer for the jurisdiction where the patient resides.

The manner and timing of reporting obligations varies depending on the communicable disease to be reported. In the event a report may be necessary; the investigator must immediately contact the IRB or the Office of Compliance for further guidance.

**The following link provide specific reporting information:**

Reporting Observed/Suspected Injuries in Research

[California Penal Code 11160](#)

Child Abuse and Neglect Reporting Act

[California Penal Code 11165](#)

Elder Abuse and Dependent Adult Civil Protection Act

[California Welfare and Institutions Code 15601](#)

[Elder Abuse and Dependent Adult Civil Protection Act Section 15630 \(a\)](#)

### **13.14 Suicidal Ideation in Research**

If research involves a study population where there is an established risk of suicidal ideation there is need for identification and management of the potential for suicide. Study participants who express suicidal intentions present a delicate situation that require attention and referral to a qualified clinician. The wellbeing and best interests of the research participant must always be maintained throughout a study.

#### **Participants and the Potential for Suicidal Risk**

The possibility of suicidal ideation or risk for suicide in an individual participant may not always be known in advance. For this reason, guidance is offered for assuring safety for both unexpected suicide risk and suspected suicide risk among research participants. In such circumstances standard mental health measures should be used in research to evaluate suicide risk.

The research team may receive information that suggests that a participant might be suicidal. If a participant reports that he/she is considering suicide, the research team is then responsible for timely and appropriate follow-up to assure the safety of that participant. It is essential that a plan to ensure that timely and appropriate follow-up of research participants who are at increased risk for potential suicide is included in the research protocol and or IRB application. Researchers are encouraged to develop

procedures, using the general guidelines, applicable to their particular research protocols.

Protocols that include the following elements require a management plan in the event suicidal ideation is identified:

- Questions regarding suicide as part of the testing, interview, or assessment protocol.
- Subject sample or research procedures that involve elements of depression or suicide risk, such as research on mood disorders, severe mental disorders, self-mutilation, debilitating illnesses, or use of a chemotherapy agent that is known to be associated with an increase of depression.

### Assessment of Suicidal Ideation

- **Intentional assessment of suicidal ideation**, through questions posed during an interview, assessment, or administration of a measurement instrument, such as the Beck Depression Inventory, due to the nature of the research. If the question is posed, either by interview or questionnaire item, be prepared to quickly review and further evaluate a positive response. The suicide question or positive response should be reviewed immediately or as soon as possible, rather than weeks or months after the data collection. This is not applicable in cases of collecting anonymous data when there is no direct subject contact, such as anonymous web-based questionnaires or questionnaires returned by mail without identifying information.
- **Unintentional assessment of suicidal ideation** may be revealed through disclosure on the part of subjects in those research projects involving subject populations or procedures that may be associated with mood disorders or in populations where it is not expected.

### Elements of Assessment

Have clinicians or trained interview/data collection staff gather additional information<sup>1</sup> to evaluate lethality or imminent danger to self and guide intervention.

- **If the person collecting the data or conducting the interview is a trained clinician**, that is, a psychologist, nurse practitioner, psychiatrist, clinical social worker, or the like, then the clinician gathers his or her own information and can act on the information as clinically indicated, (assuming the clinician has experience with managing suicide risk).
- **If the person is not a clinician or is not familiar with suicide risk management**, then a system, (including a list of readily available trained clinicians) should be in place to gather the necessary information about lethality and/or contact the appropriate clinician or make an appropriate referral for further evaluation and treatment.

An adequate assessment of lethality or imminent danger to self should, at minimum, include gathering information about the specific thoughts of suicide, whether or not the person has a plan, determine if the person has the means to carry out the plan, history of suicide attempts, family history of suicide; the person's mental health history, history of use of medication, alcohol or illicit substances that may lead to lowering of inhibitions, and the person's family or community support system.<sup>2,3,4</sup>

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<sup>1</sup> Information collected to evaluate lethality or imminent danger should not be included in research records.

<sup>2</sup> Bongar, Bruce (2002). *The Suicidal Patient: Clinical and Legal Standards of Care*. Washington D.C.: American Psychological Association.

<sup>3</sup> Jacobs, Douglas G., M.D., Editor (1999). *The Harvard Medical School Guide to Suicide Assessment and Intervention*. San Francisco, California: Jossey-Bass Publishers.

<sup>4</sup> Simpson, Skip, J.D. and Stacey, Michael, J.D. (May 2004). Avoiding the malpractice snare: documenting suicide risk assessment. *Journal of Psychiatric Practice*, 10(3), 1-5.

### Intervention

- **All staff should be trained on how to assess for suicide risk** and the emergency procedures to follow in the event someone is deemed at imminent risk of suicide. Giving research subjects a list of referrals or telling the subject to go to a hospital after disclosure or endorsement of seriously thinking about suicide would not be considered sufficient standards.

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- **If the interview or data collection is conducted by non-clinicians or research assistants**, clinical research staff should be readily available either in person, by phone, or pager response.
- If the person is evaluated as high risk for suicide, **the research staff should act quickly to protect the safety of the subject**. This may mean staying with the subject until assistance arrives or the person is transported to a hospital.

*For non-clinicians, the emergency system should outline procedures for contacting research clinicians for guidance, or in the event that clinicians are not available or cannot be contacted, the services of LAC+USC Medical Center Emergency Psychiatric Evaluation - 24-hour clinic and 911 are both available for response.*

- **For any results less than imminent risk**, research clinicians should be available to assist in developing a plan for safety with the subject. The plan for safety will depend on the level of risk and available resources.

It may include contacting the person's personal physician, making sure the subject has appropriate referrals with a plan to contact subjects as a means to evaluate the subject following through with the referrals, encouraging the person to talk to trusted family members or other community support resources, or giving the subject suicide hotline information.

For example, the clinician decides that although the subject has endorsed suicide ideation, there is no intent or plan, nor history of suicide attempts, but the subject does have bouts of depression. The clinician or clinician representative may provide the subject with referrals for treatment and the Suicide Prevention Hotline number, or discuss contacting the subject's primary physician or trusted family member to garner support or assistance.

Documentation of the assessment and procedures ultimately followed is important.



### Informed Consent Language

Inform the subjects about what will happen if they express suicidal ideation and, in particular, if they are deemed to be an imminent danger to self by way of the research informed consent process. This information would ordinarily go in the confidentiality section of the consent form or information sheet. Below is sample wording regarding the issue.

*The research team may not be able to keep confidential any disclosure or endorsement of thoughts to harm yourself. In the event that you tell the research staff that you are thinking about killing yourself or you answer yes to a question about having thoughts about suicide, the research staff will ask you more questions about the thoughts. Depending on how intense your thoughts are or how much you feel like hurting yourself, the research staff may provide you with referrals for treatment, work with you to contact your personal physician, trusted family member, or therapist to discuss your thoughts of harming yourself; or work with you on a plan that may include getting you to a hospital for safety.*

### Adverse Event Reporting and Suicidal Ideation

Adverse event reporting in research on suicide or depressed individuals needs to be tailored to the individual study. If the study involves individuals with a high risk of suicide, then a suicide would not be an “unexpected” event. Other criteria may exist, such as a hospitalization - which may require the need for IRB submission in such a case. In a study without inherent need for monitoring for depression or mood changes, a suicidal event would be unexpected, and therefore potentially reportable. Do not hesitate to contact the IRB for guidance on this issue.

### 13.15 Investigator and Staff Safety

Investigators are ultimately responsible for the conduct and safety of their research staff (including themselves). Faculty members are also responsible for safety of student researchers. Therefore, guidance for what constitutes appropriate and professional behavior must be provided before research begins. To reduce the likelihood of risks to their research team, investigators should provide training and a written management plan

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for staff who work in environments presenting high risk for injury. A good safety plan will include rules for behavior, safety and emergency situations.

Investigators are required by regulation to report “unanticipated problems involving risks to subjects or others” to the IRB (see [Section 20.2 – Unanticipated Problems Involving Risks to Subjects or Others](#)). “Others” is widely interpreted to include members of the research team, thus IRBs must evaluate risks to study staff as well as to subjects when approving a study.

The IRB may also require safety plans/guidelines be submitted and will review the adequacy of such plans before approving the research.

	<p>Chapter 14:</p> <p><b>Vulnerable Subject Populations</b></p>
<p><b>Chapter Contents</b></p>	
<p>14.1 – Protection of Children Involved as Subjects in Research (45 CFR 46 Subpart D)</p> <p>14.2 – Pregnant Women, Fetuses and Neonates in Research (45 CFR 46 Subpart B)</p> <p>14.3 – Prisoners in Research (45 CFR Subpart C)</p> <p>14.4 – Cognitively-Impaired Persons</p>	

# Chapter 14

## Vulnerable Subject Populations

This chapter addresses additional protection required when “vulnerable subjects” participate in research. Children, pregnant women, fetuses, neonates, and prisoners are vulnerable subjects as stated in the federal regulations (45 CFR 46 Subparts [B](#), [C](#), and [D](#)).

IRBs and researchers must be aware of “vulnerability” beyond the regulatory definitions. Individuals and classes of subjects may also be vulnerable depending on the research, the situation, their condition and susceptibility to coercion. Researchers are expected to take special precautions when including individuals who have a compromised ability to understand and/or are vulnerable to coercion.

### 14.1 Protection of Children Involved as Subjects in Research (45 CFR 46 Subpart D)

State and federal regulations use different terms to describe individuals below the age of consent. Federal human research regulations refer to “children”. California laws use both “minor” and “child” to refer to people under 18.

#### *Definitions Related to Children as Research Subjects*

<b>Children</b>	Individuals who have not attained the legal age to consent to research treatments or procedures. In California, the legal age is 18 years of age but there are exceptions which allow individuals under the age of 18 to consent to research and some medical procedures
<b>Minors</b>	Individuals under 18 years of age (CFC 6500)
<b>Assent</b>	A child's affirmative agreement to participate in research. Failure to object should not be construed as assent (45 CFR Part 46.402)
<b>Guardian</b>	An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care (45 CFR Part 46.402). In California, a guardian may be a parent, a legally appointed guardian, a guardian <i>ad litem</i> as appointed by a court (this is an individual who may have no relationship to the minor who is appointed by the court to protect and represent the interests of the minor before the court), or others as

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	consistent with an order of a court having jurisdiction over the minor. For wards of a court, usually an order from the judge is required in addition to permission from the person charged with care of the child
<b>Parent</b>	A child's biological or adoptive guardian
<b>Permission</b>	The authorization of parent(s) or guardian(s) to the participation of their child or ward in research
<b>Ward</b>	An individual (usually a minor) who the court has appointed a guardian to care for and take responsibility for that individual. If the minor is suffering from parental neglect or abuse, or has been involved in trouble with the law, a government agency may take temporary custody of the minor for their protection. If the custody is court-ordered, the child is a "ward of the court" or a "ward of the state."
<b>Legally Authorized Representative</b>	An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research

### Permissible Research with Children

To involve children in research, the level of risk must be justified by direct or indirect benefit. The disease or condition to be studied must be related to a research need in children. The information below describes the four permitted categories of research with minors defined by federal regulation ([45 CFR 46, Subpart D](#)).

### Permitted Categories for Research with Children

Category	Risk-benefit	Parental Permission Requirements
<b>Category 1</b> ( <a href="#">45 CFR 46.404, 21 CFR 50.51</a> )	<b>Minimal Risk</b> <ul style="list-style-type: none"><li>Research not involving greater than minimal risk</li><li>Permission from ONE parent/legal guardian may be sufficient. Assent may be required if child is 7 years of age or older</li><li><u>Usually subject to</u> Expedited level of review</li></ul>	One parent/legal guardian <b>may</b> be sufficient

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	<ul style="list-style-type: none"> <li>• Example: A study involving one venipuncture (no more than the lesser of 50 ml or 3 ml per kg in an 8-week period) in healthy 10-year-old subjects</li> </ul>	
<b>Category 2</b> <a href="#">(45 CFR 46.405, 21 CFR 50.52)</a>	<b>Greater than Minimal Risk, Direct Benefit to Subject</b> <ul style="list-style-type: none"> <li>• Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects</li> <li>• Permission from ONE parent/legal guardian <i>may</i> be sufficient <b>and</b> assent may be required if child is 7 years of age or older</li> <li>• Usually subject to Full Board review</li> <li>• Example: A Phase II study using an experimental chemotherapeutic regimen for children with malignant brain tumors for whom standard therapy has failed</li> </ul>	One parent/legal guardian <b>may</b> be sufficient
<b>Category 3</b> <a href="#">(45 CFR 46.406, 21 CFR 50.53)</a>	<b>Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject's Condition</b> <ul style="list-style-type: none"> <li>• Research involving minor increase over minimal risk greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subject's disorder or condition</li> <li>• Permission of BOTH parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent may be required if child is 7 years of age or older</li> <li>• Subject to Full Board review</li> <li>• Example: A study testing new biomarkers of disease progression that involves 2 extra</li> </ul>	Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.

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	samples of cerebrospinal fluid over a year of therapy (beyond the 5-6 that would be done as part of the child's routine care.)	
<p><b>Category 4 –</b>  <a href="#">(45 CFR 46.407 21 CFR 50.54)</a></p> <p><i><b>NOTE: A category 4 study is very rarely approved.</b></i></p>	<p><b>Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children's Health or Welfare</b></p> <ul style="list-style-type: none"> <li>• Research not otherwise approvable which presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children</li> <li>• The Secretary of the U. S. Department of Health and Human Services, after consultation with a panel of experts and following an opportunity for public review and comment, must either approve or deny approval of the study.</li> <li>• Permission of BOTH parents/legal guardians is required, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent of child (if child is 7 years of age or older).</li> <li>• Subject to Full Board review and DHHS review as described above</li> <li>• Example: A study examining sleep mechanisms in children to better understand sleep-related diseases. Involves 13- to 17-year-old adolescents undergoing 3 hospital visits for IV infusion of acetate and glucose followed by MRI, in normal and sleep-deprived groups. [See OHRP's "Special Protections for Children as Research Participants" for more information about the above and other examples of the handful of studies reviewed in this category nationwide]</li> </ul>	<p>Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.</p>

### Permission from Parents and Assent from Children

The term permission refers to legally binding authorization granted by parents or guardians to enroll a minor in research. In most cases, permission from one or both parents/guardians must be obtained for their child/ward to participate in a research study. Circumstances in which parental permission may be unnecessary or inappropriate are discussed below under Waiver of Parental Permission.

For children/subjects, the term used is **assent**. Typically, children do not have the legal capacity to consent to participate in research, but children should be involved in the process if they are able to assent. Assent meaning - capable of having a study explained to them and/or reading a simple form about it, and giving verbal or written agreement to decide to participate in the study. Circumstances in which a child's assent may be unnecessary or inappropriate are discussed below under Waiver of Child's Assent.

### Consent Guidelines for Children by Age Group

Age of Participant	Assent Form Recommended	Parental Permission Form Recommended
Infant-6 years old	No	Yes
7-13 years old	Yes	Yes
14-17 years old	Yes	No (add signature line to adolescent assent form for parent(s) to sign)
13-17 years old	Yes	Yes

### When One Parent's Permission Is Sufficient

For certain research the IRB may determine that permission from only **one** parent is sufficient. Agreement from two parents is required unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child [[45 CFR 46.406](#), [45 CFR 46.407](#), [21 CFR 50.55\(e\)](#)].



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When there is only one living parent or guardian or one parent has sole custody after a divorce, the PI may determine that single-parent or single-guardian permission is sufficient.

### **When Parents Disagree**

If parents disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. When both parents are involved in the decision, they must agree for the child to be enrolled.

### **Waiver of Parental Permission**

In certain cases, parental permission is not a reasonable requirement to protect subjects (neglected or abused children); more detailed examples are given below. The IRB will consider requests for waiver of parental permission on a case-by-case basis. For FDA regulated research a waiver may be granted for expedited review/minimal risk research. For non-FDA-regulated studies, the IRB may waive parental/guardian permission provided “an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law” ([45 CFR 46.408](#)).

Additionally, Public Demonstration Projects may obtain a waiver of parental permission if the IRB finds that all criteria below are satisfied:

- The research is to be conducted by or subject to the approval of state or local government officials, and
- The research is designed to study, evaluate or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs, and
- The research could not practicably be carried out without the waiver or alteration, and
- The research is not FDA-regulated.

### **Examples where parental permission *may* be waived:**

- Research on child abuse or neglect, or research that is reasonably likely to elicit information identifying child abuse or neglect, where there is serious doubt as to whether the parents' interests reflect the child's interests [[45 CFR 46.408\(c\)](#)].
  - The Federal Regulations specifically refer to “research on neglected or abused children” as an instance where “parental or guardian permission is not a reasonable requirement to protect the subjects,” the IRB would be likely to waive parental permission in such a case, provided the other requirements of the regulations [[45 CFR 46.408\(c\)](#)] are met.
- Research on people under age 18 who are in circumstances where they are clearly outside of parental influence or control.
  - Researchers also should be aware that some people under 18 who are living independently may not fit the federal definition of “children” and are able to consent for themselves without a waiver of parental permission. See [California Exceptions Permitting Certain Minors to Consent](#) below.

### **Waiver of Child Assent**

In certain cases, the IRB may waive the requirement to obtain children's assent, for example:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted, or
- The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research ([45 CFR 46.408](#), [21 CFR 50.55](#))

Assent may not be required but should always be sought.

The parents' right to make medical decisions for their child may come into conflict with the child's right to give or withhold assent. In this situation, assent may not be mandatory, though it always should be sought.

If the child is considered capable of being involved in the informational process, a simple verbal explanation of what will happen to him/her and the opportunity for questions and

discussion should always be provided. Even if the requirement for assent is waived, it is always preferable to seek the child's assent if possible. There must be documentation on the parental permission form or in the study records that the child was appropriately informed about the study.

**NOTE: Parental Permission for children's enrollment cannot be waived for FDA-regulated studies except for the use of an FDA test article meeting the emergency exception** or a study involves no more than minimal risk, and meets the criteria set forth in the following guidance: ["IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects"](#)

### **Waiver or Alteration of Informed Consent in Studies Involving No More than Minimal Risk**

The IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or may waive the requirement to obtain informed consent or assent if the following is found and documented:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Please see the guidance document for more information: ["IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects"](#)

### Children under Guardian Care

In California, a guardian normally has the same authority with respect to the child as a parent having legal custody, except as limited by statute or court order (the legal document establishing the guardianship). This includes the authority to consent on behalf of the child to general medical care.

For research that involves medical care, however, a guardian's authority to consent or require is restricted, in the absence of an affirmative court order, in the following circumstances:

- By the terms of any letters of guardianship issued by a court (a certified copy of which should be obtained and placed in the medical record)
- For surgery on a child 14 years or older, unless:
  - The child also consents;
  - The guardian obtains a court order, or
  - The guardian has determined based on medical advice that an emergency exists in which the child faces loss of life or serious bodily injury if the surgery is not performed.
- From administering an “experimental drug” (defined in Health & Safety Code Section 111515; FDA investigational drug), unless a 7 years or older child also consents and the drug is related to maintaining or improving health or obtaining information about a pathological condition of the child
- From authorizing electro-convulsive treatment (defined in [Welfare & Institutions Code Section 5325](#))
- From admitting the child to a “mental health treatment facility” [defined in [Probate Code 2356\(a\)](#)] without the child's consent
- From authorizing antipsychotic drugs except under certain circumstances
- From authorizing an elective procedure performed primarily for the purpose of rendering the child sterile (not treatment which secondarily results in sterilization)
- From authorizing psychosurgery under any circumstances

For additional information regarding informed consent considerations, refer to “[Informed Consent for Children Not in Parental Custody](#)” below.

### **Children under the Jurisdiction of Dependency Court / Court Appointee**

Parental permission and consent for a child’s participation in research is not required when the juvenile dependency court has explicitly removed the individual parents’ power to make such a decision. In cases where the parent has lost parental rights, the IRB can accept consent from whomever the court appoints as authorized under applicable state or local law to consent on behalf of a child to general medical care.

If the research involves children who are wards of the state, investigators should contact the Office of Compliance. Research involving greater than minimal risk and the prospect of participant direct benefit to wards may be approved by the IRB. Research which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved only if:

- There is a court appointed advocate for each child who:
  - May be the same individual for all of the children
  - Has the background and experience to act in (and agrees to act in) the best interest of the child for the duration of the research, and
  - Is not associated in any way with the research (except as an advocate), the investigators, or any guardian association

Additionally, for research involving medical care for wards of a court, often an order from the judge is required, in addition to permission from the person charged with the care of the child.

Before waiving the parental consent requirement, the IRB should require a court order that clearly and specifically provides that the children may participate in research without parental consent. According to [California Welfare and Institutions Code Section 361 \(a\)](#) there is no limitation of parents’ right to consent to research that was not “necessary to protect the child.”

### Informed Consent for Children Not in Parental Custody

Investigators are required to obtain a court order permitting the participation of the individual subjects/class subjects in the research without parental consent, and are required to follow the procedure in [Los Angeles County Superior Court Rule Chapter 7](#) (if research and the children are within Los Angeles County) or other applicable court procedures.

The investigators are required to obtain the assent of subjects unless the IRB determines that assent should not be obtained in accordance with federal human subjects regulations.

### California Exceptions Permitting Certain Minors to Consent

In California, minors (those under 18 years of age) generally may not consent to medical care or treatment, or research involving medical care or treatment, without a parent or legally authorized representative (LAR). Federal regulations when interpreted with California legal exceptions allow minors to consent as adults to research or treatment.

The following categories of minors are permitted to consent as adults to research or treatment:

- Emancipated minors in California have the legal right to consent on their own behalf to medical, dental, or mental health treatment. They also have extensive rights to enter into legal and business arrangements, or participation in research ([Section 7000-7143](#)):

Emancipated minors may be:

- married or divorced, or
- on active duty in the U.S. armed forces
- emancipated by a court

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- **Self-Sufficient minors:**
  - 15 years of age or older, and
  - living separate from their parents/guardians, and
  - managing their own financial affairs
  - may consent to the minor's own medical or dental care (Section 6922)
- **Minors, 12 years or older, seeking care for:**
  - Prevention or treatment of pregnancy
  - Out-patient mental health treatment or counseling, excluding drugs
  - Care related to the diagnosis or treatment of reportable infectious, contagious, or communicable/sexually transmitted diseases
  - Care provided to the victims of sexual assault or rape
  - Medical care and counseling relating to the diagnosis and treatment of drug or alcohol abuse (only if treating physician deems and documents that parental involvement is inappropriate), excluding narcotic replacement drugs.

With IRB approval, for the above categories a minor must provide consent and sign the consent form just as an adult would, unless the IRB approves a waiver or alteration of the usual consent standards for adults. The IRB requires that any investigator that is not familiar with these laws and proposes to enroll a minor without parental permission to contact the IRB staff for further guidance. The IRB always retains the option to exclude minors that may otherwise consent in light of risks or the nature of the trial.

Researchers enrolling participants in other states or countries must comply with local law. In all cases, if the prospective subjects cannot legally consent for the treatments or procedures involved in the study because they are too young, they are considered "children" by federal regulations. If they can consent for the treatments or procedures, they are not "children" by federal regulations (therefore if they are not "children" 45CFR46 subpart D does not apply).

### Managing Disclosure of Sensitive Information

In the course of research investigators may explore such topics as STDs, use of illegal substances, HIV status. The investigator may be required to disclose sensitive information during the course of a study. The permission and/or assent form should describe plans for disclosure—or non-disclosure—of such information to parents, legal authorities, and the subjects themselves.

In some cases, it may be appropriate for the PI to seek an NIH Certificate of Confidentiality (refer to [Section 11.4 – Certificate of Confidentiality](#)).

Also visit <http://grants.nih.gov/grants/policy/coc/background.htm> for information as to whether a certificate is applicable for a particular study.

### Mandatory Reporting

Discovery of child abuse initiates certain ethical and legal obligations. In most cases, the same reporting expectations pertain in research settings as in clinical settings. University researchers may be health professionals or other “mandated reporters” under the California Child Abuse and Neglect Reporting Act ([California Penal Code 11164-11174.3](#)). Even if the mandated reporter status is not clear, the investigator can make a voluntary report to the appropriate agency. Please refer to the following USC policy for details and guidance: <http://policy.usc.edu/mandated-reporters/>. See also USC policy on Protecting Minors at: <https://policy.usc.edu/protecting-minors/>

If an investigator is planning a study that is designed or likely to elicit information about sexual or physical abuse of a child, the application and consent/assent forms must indicate how discovery of such information will be handled.

If such information is discovered unexpectedly (not anticipated given the study design or subject population), the PI should contact the Los Angeles County Department of Children and Family Services (800) 540-4000 and the Office of Compliance.

### Enrolling Children in Long-Term Studies

Long-term research studies may involve subjects who are children at the time of enrollment but reach the age of consenting (18 years old, in California) while study



procedures or follow-up are still ongoing. The IRB will consider on a study-by-study basis whether obtaining new consent from such subjects is required.

If there is continued interaction with subjects who were first enrolled as children, “re-consenting” when a subject’s legal status changes will usually be required. If the only continuing study procedures are follow-up activities such as review of records or examination of biological specimens, the original consent may suffice.

### Research Involving Children in Educational Settings

When planning studies involving children in educational settings, investigators should consider the following issues:

Researchers must be aware of district policy of the school in which they intend to do research. District policy dictates who gives permission and what kind of research can be conducted. For the participation of individual children in research only a parent or a legally authorized representative (LAR) may grant permission to approach the child to participate in research.

If the study will be conducted during school hours, an equivalent alternative activity should be offered for students who do not wish to participate.

Additionally, according to [California Education Code 51513](#), generally speaking, no test, questionnaire, survey, or examination containing any questions about the pupil's personal beliefs or practices in sex, family life, morality, and religion, or any questions about the pupil's parents' or guardians' beliefs and practices in sex, family life, morality, and religion, shall be administered to any pupil in kindergarten or grades 1 to 12, inclusive, unless the parent or guardian of the pupil is notified in writing of any of these procedures.

### FERPA Rules and Research with Education Records

The Family Educational Rights and Privacy Act (FERPA) (34 CFR 99) sets limits on the conditions under which education records can be accessed for research purposes.

Education records are generally defined in FERPA as personally identifiable information regarding a student in a K-12 or higher education setting that receives federal funding.

It is the holder of the records (e.g., a school authority, university registrar) –not the researcher – who carries the legal responsibility for abiding by FERPA. Therefore, it is

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the holder of the records—not the researcher – who is in violation of FERPA if education records are released inappropriately or illegally.

It is not the responsibility of the IRB to ensure that researchers access personally identifiable student level data in compliance with FERPA. It is up to the researcher to ensure that the personally identifiable information from an education record will not be disclosed to any other party without prior consent of the parent or eligible student. If a researcher improperly discloses personally identifiable information from an education record, the researcher may not be allowed to access information from education records for five years (34 CFR 99.33(e)). Please see FERPA for more information regarding researcher responsibilities: <http://www.ed.gov/policy/gen/guid/fpco/ferpa/index.html>.

FERPA requires that the holder of the records ensure written consent is obtained from a parent or eligible student in order to release personally identifiable student information. The holder of the record only obtains consent from parents and eligible students under limited circumstances (see the Directory Information Policy exception below).

There are exceptions to FERPA that might also enable a researcher to access personally identifiable student information without obtaining consent from the parent or eligible student. The holder of the record *may* release the records to the researcher under the following conditions:

- The researcher is conducting studies *for or on behalf* of the school or district (34 CFR 99.31(a)(6))
- The information is identified by the school within its Directory Information policy (34 CFR 99.31(a)(11))

Consent is not required if the information requested for release is not personally identifiable (therefore has been stripped of any identifying information).

Individuals who are employed by schools or universities in one role (e.g., teacher, administrator, superintendent, academic advisor) and who are conducting research as part of their graduate level coursework (e.g., masters thesis or dissertation) must abide by FERPA when seeking to access personally identifiable student information. In other words, for the purposes of accessing student information *as a researcher*, they must ensure that they seek parent or eligible student consent or that they are able to access the information as the result of one of the aforementioned exceptions. They may not use their access through their employment in order to obtain personally identifiable information.

### **PPRA Role in Research Supported by Department of Education**

USC Office of Compliance and outside legal counsel have determined that there is no IRB role in applying the Protection of Pupil Rights Amendment (PPRA) to human subjects research. Complying with PPRA is the responsibility of the school system/district (per internal communication dated 3/20/14).

It is the responsibility of the researcher/school that research funded by the Department of Education complies with additional protections under the Protection of Pupil Rights Amendment (PPRA) (34 CFR Part 98).

Schools and contractors must obtain prior written parental consent before minor students are required to participate in any survey, analysis, or evaluation funded by the Department of Education.

### **Research Supported by the Department of Defense (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart D with the following modification:

- The DOD does not apply Subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DOD supported research.

### **14.2 Pregnant Women, Fetuses and Neonates in Research (45 CFR 46 Subpart B)**

Federal regulations mandate that IRBs require additional safeguards before approving research involving pregnant women, human fetuses, neonates of uncertain viability, or non-viable neonates. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

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Subpart b provides for scientific judgment, determination of risk versus benefit, who may not participate, consent requirements and, who may make determination of viability. The links are provided below:

Research Involving Pregnant Women or Fetuses - [45 CFR 46.204](#)

Research Involving Neonates - [45 CFR 46.205](#)

Research Involving After Deliver, The Placenta, The Dead Fetus or Fetal Material – [45 CFR 46.206](#)

### **Newborn Dried Bloodspots**

The Newborn Screening Saves Lives Reauthorization Act of 2014 explicitly states that the use of newborn dried bloodspots for research is considered to involve human subjects if the research is federally supported and the bloodspots are collected on or after March 18, 2015. The identifiability (or not) of the bloodspots is irrelevant. In other words, if a researcher is receiving de-identified or anonymous bloodspots for research, the research is considered to involve human subjects. A detailed summary of recommendations is provided by the U.S. Department of Health and Human Services, Secretary's Advisory Committee on Human Research Protection (SACHRP). The goal of this recommendation is to provide thoughtful consideration of this act and allow for important research to take place. Refer to: <https://oprs.usc.edu/files/2016/05/SACHRP-Newborn-Dried-Bloodspots.docx>

### **14.3 Prisoners in Research (45 CFR 46 Subpart C)**

Because incarceration affects a person's ability to make a truly voluntary decision whether or not to participate in a research project, state and federal regulations provide additional safeguards for the protection of prisoners in research. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

Research involving prisoners is never exempt from IRB review. Any study that recruits prisoners that does not qualify for expedited review must be reviewed at a fully-convened

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IRB meeting with a prisoner representative present for the discussion and vote of that study protocol. The IRB Chair and/or IRB Director, and/or IRB Staff ensure a prisoner representative and/or consultant will be present at the meeting.

Apart from their membership on the IRB, the majority of the IRB members (exclusive of prisoner representative) shall have no association with the prison(s) involved in the research being reviewed. If research activities under the jurisdiction of the USC IRB involve prisoners held outside of the state of California, the investigator is responsible for identifying and ensuring compliance with the laws of that state.

### **Additional PI Responsibilities**

Under [28 CFR 512](#) the Federal Bureau of Prisons places special restrictions on research that takes place in the Bureau of Prisons. The regulations specify additional requirements that must be addressed by the PI to obtain approval for Bureau of Prison based research.

The California Department of Corrections and Rehabilitation (CDCR), [Title 15](#), (California Code of Regulations) requires that research that takes place in the department facilities be submitted by the PI to the departments research advisory committee for review and approval.

It is the investigator's responsibility to identify and meet these requirements.

### **Federal Regulations Permit 5 Categories of Research with Prisoners ([45 CFR 46.306](#))**

The 5 permitted categories are:

- i. Studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects
- ii. Studies of prisons as institutional structures or of prisoners as incarcerated persons provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

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- iii. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of HHS (through OHRP) has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of their intent to approve such research
- iv. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research
- v. Waiving the applicability of [45 CFR 46.305\(a\)\(1\)](#) and [45 CFR 46.306\(a\)\(2\)](#) for certain research conducted or supported by HHS. This is referred to as the **Epidemiology Waiver**. In specific, for HHS conducted or supported research involving epidemiologic studies: (1) In which the sole purposes are (i) To describe the prevalence or incidence of a disease by identifying all cases, or (ii) To study potential risk factor associations for a disease, and (2) Where the Institution responsible for the conduct of the research certifies to OHRP, acting on behalf of the Secretary, that the IRB approved the research and fulfilled its duties under [45 CFR 46.305\(a\)\(2\)-\(7\)](#) and determined and documented that (i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and (ii) Prisoners are not a particular focus of the research. (For more information, refer to: <http://www.gpo.gov/fdsys/pkg/FR-2003-06-20/html/03-15580.htm>)

The informed consent form must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on their duration of incarceration or terms of parole. The IRB must determine whether assent is a requirement for research pertaining to prisoners that are children.

### **IRB Considerations for Prisoner Subjects (45 CFR 46.305)**

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find:

1. The research under review represents one of the categories of research permissible under [45 CFR 46.306\(a\)\(2\)](#).
2. Any possible advantages accruing to the prisoner through their participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that their ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project
5. The consent information is presented in language which is understandable to the subject population
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on their parole
7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences. Subjects must be adequately informed of this fact.

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If the research is conducted or supported by HHS, the University must certify to the HHS Secretary (through OHRP) that the IRB has approved the research under the HHS regulations for research that involves prisoners as participants. Additionally, the HHS Secretary (through OHRP) must determine that the research meets one of the approvable categories before the research can be initiated. This determination is known as the “OHRP Prisoner Research Certification”.

### *Helpful Links*

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- OHRP Guidance on the Involvement of Prisoners in Research:  
<http://www.hhs.gov/ohrp/policy/prisoner.html>
- OHRP Frequently Asked Questions – Prisoner Research:  
<http://answers.hhs.gov/ohrp/categories/1568>

### *Definitions Related to Prisoners as Research Subjects*

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<b>Prisoner</b>	Any individual involuntarily confined or detained in a penal Institution; individuals sentenced to such an Institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal Institution and individuals detained pending arraignment, trial, or sentencing.
<b>Prisoner Representative</b>	Any individual who can represent the concerns that prisoners might have about research, who has a working knowledge of prison conditions and the life of prisoners, such as an individual employed at a prison, a prisoner chaplain, a social worker who deals with prisoners, or a prisoner advocate
<b>Penal Institution</b>	Any place of confinement for convicted criminals. Penal Institutions include local and county jails and workhouses, reformatories, penitentiaries, prison camps and farms, as well as the modern correctional Institution.
<b>Parolees and Probationers*</b>	<p>Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.</p> <p>Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise</p>



about research involving these populations.

The Office for Human Research Protection (OHRP), provides specific regulatory definitions for circumstances pertaining to parolees and probationers. The following are examples of application. Refer to [OHRP Prisoner Research FAQs](#)

### Subjects Who Later Become Incarcerated

If a study was not initially approved to recruit prisoners, the investigator may not enroll prisoners. A prisoner, who is brought to USC for treatment and happens to be eligible for a research study, may not be enrolled in a study unless: the study was approved to include prisoners, and a prisoner representative was present during the discussion and vote of the study.

The regulations for research with prisoners apply to any subject who becomes a prisoner after enrolling in research. It is unlikely that the IRB contemplated the constraints imposed by incarceration during their review therefore, if an investigator determines that a subject has become a prisoner after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or an amendment request must be submitted for the inclusion of prisoners as subjects. With the exception of special circumstances, all research interactions and interventions with, and collection of identifiable private information about, the now-incarcerated subject must cease until all the requirements of [Subpart C](#) have been satisfied. The Office for Human Research Protections (OHRP) guidance allows in special circumstances, for which the Principal Investigator (PI) asserts that it is in the best interest of the subject to remain in the research study while incarcerated; the IRB Chair may determine that the subject can continue to participate in the research until the requirements of [Subpart C](#) are satisfied.

### Limits under California Penal Code

Under the California Penal Code, competent adult prisoners are permitted to decide whether or not to participate in behavioral research, but no biomedical research can be conducted on any prisoner in the state. See [Cal. Penal Code §§ 3501, 3502](#) (also, see definitions for “biomedical” and “behavioral research” at § 3500). Prisoners may,

## Chapter 14: Vulnerable Subject Populations

however, obtain investigational drugs or treatments – under a protocol or treatment Investigational New Drug (IND) application – if a physician determines that the drug or treatment is in the best interest of the patient/prisoner and the prisoner gives consent [id. § 3502.5](#). With regard to behavioral research, generally, informed consent must be obtained, but can be waived if it is determined that it would be unnecessary or would significantly inhibit the research [id. § 3505](#). There are specific state law requirements with regard to consent for prisoners, see [id. §3521](#). Additional federal guidelines that pertain to prisoners in research are outlined below. Note, however, that in some instances the federal guidelines conflict with California law.

For more information, review the California Penal Code and guidance links below.

### *Helpful Links*

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- CA Penal Code 3501-3509.5:  
[https://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=2.&article=](https://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=2.&article=)
- CA Penal Code 3515-3520:  
[http://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=3.&article](http://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=3.&article)
- CA Penal Code 3521-3523:  
[https://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=4.&article=](https://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=4.&article=)
- CA Penal Code 3524  
[https://leginfo.legislature.ca.gov/faces/codes\\_displaySection.xhtml?sectionNum=3524.&lawCode=PEN](https://leginfo.legislature.ca.gov/faces/codes_displaySection.xhtml?sectionNum=3524.&lawCode=PEN)
- CA Code of Regulations, Title 15, Article 9.1 “Research of Inmates/Parolees”  
[http://www.cdcr.ca.gov/Regulations/Adult\\_Operations/docs/Title15-2016.pdf](http://www.cdcr.ca.gov/Regulations/Adult_Operations/docs/Title15-2016.pdf)
- CA Department of Corrections and Rehabilitation (CDCR) guidance “Research Involving Wards, Inmates or Staff”  
[http://www.cdcr.ca.gov/Reports\\_Research/researchWIS.html](http://www.cdcr.ca.gov/Reports_Research/researchWIS.html)
- CA CDCR guidance: “Research Project Approval Guidelines”

[https://www.cdph.ca.gov/Programs/CID/DOA/CDPH%20Document%20Library/RPT2010\\_01HIVAIDSLaws2009\\_ADACompliant.pdf](https://www.cdph.ca.gov/Programs/CID/DOA/CDPH%20Document%20Library/RPT2010_01HIVAIDSLaws2009_ADACompliant.pdf)

### 14.4 Cognitively-Impaired Persons

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur during situations associated with high levels of stress (death of a family member). Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally-impaired. Some research questions may be answered only by research that involves persons with impaired decision-making capacity.

Unlike research involving children, prisoners, pregnant women, and fetuses, HHS regulations do not specifically address research involving persons who are cognitively-impaired. While limited decision-making capacity should not always prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population. Subjects with permanent or transient cognitive impairments may find it difficult to understand the difference between research and treatment, and to differentiate between investigators' multiple roles and interests (practitioner and researcher).

#### IRB Criteria for Reviewing Research with Cognitively-Impaired Persons

The IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons:

- Research not involving greater than minimal risk
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- The risk is justified by the anticipated benefit to the subjects
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

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- Adequate provisions are made for soliciting the assent of the subject and permission of their legally authorized representative

The IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons when the research is greater than minimal risk, there is no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition:

- The risk represents a minor increase over minimal risk
- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition
- Adequate provisions are made for soliciting assent of the subject and permission of their legally authorized representative

### Assessing Capacity to Consent

A key factor in subjects' decision-making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally. Assessment is complex and there are no standard criteria for determining capacity to consent to research. Individual capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. IRB applications for the proposed involvement of cognitively impaired subjects should propose a plan to screen for incapacity in subjects who are likely to be incapable of providing consent. Assessments should be timed to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

### Consenting Cognitively-Impaired Subjects

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may

## Chapter 14: Vulnerable Subject Populations

include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject enrolls.

The consent process should be ongoing to ensure subjects' ability understand and follow the protocol. The IRB, at its discretion, may observe the consent process or require an outside witness to observe the consent process.

Investigators are encouraged to review "Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment." (The American Journal of Psychiatry, 155:11, 1998) and, "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity" (The National Bioethics Advisory Commission's report, 1998).

### **Voluntariness, Consent, and Assent**

In addition to determining subjects' ability to consent, investigators must also ensure subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject.

In conclusion, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be necessary in certain circumstances. Treating all individuals who have cognitive deficits as capable, at times, of understanding research is respectful of their autonomy. It also exemplifies the principle of "respect for persons" in The Belmont Report. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

### **Surrogate Consent**

If a potential subject is found to be incapable, the federal regulations allow a "Legally Authorized Representative" to consent on their behalf. The federal regulations leave it to the states to define this term. In California, the selection of an appropriate representative to consent on behalf of those unable to consent for themselves is clearly delineated. The

IRB has determined that the individuals defined in the state of California Health and Safety Code, [Section 24178 \(c\) and \(d\)](#), as legally authorized representative meet the HHS and FDA definitions of legally authorized representative. These rules only apply to medical experiments that relate to the cognitive impairment, lack of capacity or serious or life-threatening disease or conditions of research subjects.

### **Cognitively-Impaired in Non-Emergency Room Environments**

The research covered is that of medical experiments that “relate to the cognitive impairment, lack of capacity, or serious life-threatening diseases and conditions of research subjects.” If a person is unable to consent and does not express dissent or resistance to participation in such research, surrogate informed consent may be obtained from a surrogate decision-maker with reasonable knowledge of the subject. The proxy decision maker is to use a “substituted judgment” standard if possible; if not, a “best interests” standard. The proxy shall include any of the following persons, in the following descending order of priority:

- a) The person's agent pursuant to an advance health care directive
- b) The conservator or guardian of the person having the authority to make health care decisions for the person
- c) The spouse of the person
- d) An individual as defined in Section 297 of the Family Code (a “domestic partner”)
- e) An adult son or daughter of the person
- f) A custodial parent of the person
- g) Any adult brother or sister of the person
- h) Any adult grandchild of the person
- i) An available adult relative with the closest degree of kinship to the person

When there are two or more available persons who may give surrogate informed consent and who are in the same order of priority, if any of those persons objects to have the subject participate in the medical experiment, consent shall not be considered as having

been given. Also, consent of a person who is in lower priority cannot supersede the refusal to consent by a person who is a higher priority surrogate.

### **Cognitively-Impaired in Emergency Room Environments**

Surrogate informed consent may be obtained from a surrogate decision maker who is any of the following persons:

- The person's agent pursuant to an advance health care directive
- The conservator or guardian of the person having the authority to make health care decisions for the person
- The spouse of the person
- An individual defined in [Section 297](#) of the Family Code (a “domestic partner”)
- An adult son or daughter of the person
- A custodial parent of the person
- Any adult brother or sister of the person

When there are two or more available persons described in the above list, refusal to consent by one person shall not be superseded by any other of those persons.

Note that the rules on proxy consent in this statute do not apply to subjects who lack capacity to give informed consent and are involuntarily committed, voluntarily admitted, or admitted on conservator-request to a psychiatric hospital. Investigators should consult the IRB for guidance when the potential subjects are in one of the above categories.

## Chapter 15: Biomedical Research

### Chapter Contents

- 15.1 – Chart Review / Case Studies
- 15.2 – Specimens (Human Biological Materials)
- 15.3 – Repositories: Banking of Specimens/Data
- 15.4 – NIH Genomic Data Sharing Policy (GDS)
- 15.5 – Genetic Research
- 15.6 – Pregnancy Testing in Research
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# Chapter 15

## Biomedical Research

This chapter discusses special types of biomedical research and additional requirements for investigators conducting these types of research.

### 15.1 Chart Reviews / Case Studies

#### Chart Reviews

Reviewing medical charts or records for research purposes requires IRB review and approval. The level of IRB review depends on the nature of the data collected, if any identifying information is recorded, and whether study data already exist (retrospective) or will be created in the future (prospective). In the iStar application, investigators are asked to provide the range of dates for the data and a list of the specific data fields that will be extracted from medical records.

The IRB may authorize a waiver of informed consent for chart review research when the following criteria are met:

- The study involves no more than minimal risk to participants
- The waiver will not adversely affect the rights and welfare of participants
- The research could not practicably be carried out without the waiver
- When applicable, participants are provided with additional pertinent information after participation.

The IRB may also waive the requirement for a Health Insurance Portability and Accountability Act (HIPAA) authorization for chart review research if the [following criteria are met](#):

1. The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following:

- a. An adequate plan to protect the identifiers from improper use and disclosure
  - b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or retention is required by law
  - c. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information is permitted
2. The research could not practicably be conducted without the alteration or waiver or alteration
  3. The research could not practicably be conducted without access to and use of the protected health information.

HIV test results cannot be recorded for chart review research conducted under a waiver of HIPAA authorization. For more information, refer to [Section 11.5 – Health Insurance Portability and Accountability Act \(HIPAA\)](#).

### Case Studies

At USC, the collection of data from **more than three** individuals is considered to be human subjects research and must be submitted to the IRB.

If data collected is de-identified, then HIPAA and state laws do not apply, and no HIPAA Authorization is needed. HIPAA regulations apply to collection of protected health information, even though the case study does not require IRB review. The HIPAA Authorization Form (generic template) may be customized for case studies if necessary. For additional information refer to [HIPAA Privacy Rule: Policies, Forms and Other Resources](#) and [Section 11.5 – Health Insurance Portability and Accountability Act \(HIPAA\)](#).

### 15.2 Specimens (Human Biological Materials)

Human biological materials include blood, urine, saliva, hair, nails, cells, tissue samples (fresh, frozen, or paraffin blocks), other body fluids or tissues, and molecules derived from these materials. Common sources of specimens used in research include:

- Specimens to be collected specifically for a research project
- Specimens collected during previous research projects
- Stored (archived) tissue from diagnostic testing or surgery
- Tissue that is discarded during routine medical care
- Specimens obtained from repositories at USC or outside Institutions
- Specimens purchased from commercial tissue banks

The use of human biological materials in research requires review by the IRB. The level of review depends on the potential risks to participants, how the specimens were collected or will be collected, and what information is associated with the specimens. Some specimen research may require Full Board review, other research may qualify for expedited review, and some research may be granted exempt status. Refer to [Chapter 7 – Types of IRB Submissions](#) for the expedited and exempt review categories that specifically refer to specimens. The IRB makes the determination about the appropriate review type, not the investigator.

Specimen research involves the potential risk of loss of confidentiality. The level of risk is determined by the type of information obtained with the specimen. Specimens are generally labeled in one of three ways:

- **Identified:** The specimen is directly labeled with personal identifying information (such as a name, patient number, or medical record number)
- **Coded:** The specimen is labeled with a code that researchers can link to personal identifying information
- **Anonymous:** The specimens are not labeled with direct identifiers or a code; researchers cannot retrieve any personal identifying information

Specimens that are truly anonymous carry no risk of loss of confidentiality. Specimens that have direct identifiers carry the greatest risk of loss of confidentiality. Whenever possible, investigators should obtain anonymous or coded specimens to minimize potential risks.

Investigators who obtain coded specimens but do not hold the link to identifiers and cannot obtain identifiable information about the participants are not conducting human subjects research per [OHRP Guidance on Research Involving Coded Private Information or Biological Specimens](#). At USC, investigators may submit this type of research to the IRB using the “Coded Specimens/Data” review form in the iStar application.

Research that uses only cadaver specimens is not considered human subjects research under federal regulations. Research that uses only anonymous specimens is also not considered human subjects research. Investigators conducting research on these types of specimens do not need to submit the research to the IRB.

### **Newborn Dried Bloodspots**

The Newborn Screening Saves Lives Reauthorization Act of 2014 explicitly states that the use of newborn dried bloodspots for research is considered to involve human subjects if the research is federally supported and the bloodspots are collected on or after March 18, 2015. The identifiability (or not) of the bloodspots is irrelevant. In other words, if a researcher is receiving de-identified or anonymous bloodspots for research, the research is considered to involve human subjects. A detailed summary of recommendations is provided by the U.S. Department of Health and Human Services, Secretary’s Advisory Committee on Human Research Protection (SACHRP). The goal of this recommendation is to provide thoughtful consideration of this act and allow for important research to take place. Refer to: <https://oprs.usc.edu/files/2016/05/SACHRP-Newborn-Dried-Bloodspots.docx>

### **Retaining Specimens for Future Research**

If specimens obtained in a study will be retained for future use in other studies, the informed consent form must disclose this to participants. The consent form should describe who might have access to specimens and information in the future, the potential purposes of the future specimen research, how participants can request destruction or removal of their specimens from future research use, and whether there are plans to compensate participants if a commercial product is developed from use of their

specimens. Participants should be given the opportunity to opt out of storing samples for future research.

### Material Transfer Agreements (MTAs)

Transfer of materials among collaborators requires the use of **Material Transfer Agreements (MTAs)**. MTAs ensure USC's rights are protected when specimens or reagents are shared with colleagues or private entities.

An MTA is a research contract between a provider and recipient of research materials which governs the terms and conditions under which the material may be used. An MTA protects the intellectual and other property rights of the provider and generally addresses:

- Limits on the use of the research materials, inventions, and results
- Prohibitions on the redistribution of the material
- Conditions of use, including prohibitions of use in animals or humans
- Conditions for publication, usually with provisions that the manuscript must be seen by the donor before submission for publication
- A hold-harmless clause, meaning that the donor has no liability resulting from the use of the material
- The return of unused materials

There are two main types of MTAs: incoming and outgoing. MTAs at academic Institutions fall into these categories:

- Transfers between academic or non-profit research Institutions
- Transfers from industry to academia
- Transfers from academia to industry

USC is a member of the Uniform Biological Material Transfer Agreement which was developed by the NIH to encourage the signatory Institutions to share research materials.

MTAs need to be reviewed to ensure compliance with USC policies, principles and guidelines, and all MTAs must be signed by an authorized representative of USC.

Review and approval of MTAs is conducted by the Senior MTA Administrator of the USC Stevens Institute (<https://stevens.usc.edu/researchers/mta-cda/>).

Additionally, IRB review and HIPAA consideration may apply when human specimens that contain identifiable subject information are transferred among Institutions.

### 15.3 Repositories: Banking of Specimens / Data

The banking of specimens/data refers to the creation of tissue banks and/or databases (repositories) to collect, store, and distribute human specimens and data for future research purposes. Repository activities involve three components:

- **Collection** of specimens/data
- **Storage and management** of the specimens/data
- **Distribution** of specimens/data to “recipient” investigators for use in future research projects

#### **Research Repositories**

If specimens or data were collected for research purposes, it is a research repository. Collection of specimens/data, repository storage or data management, and use of specimens or data are all considered research activities and require IRB review and approval.

#### **Repository Data Not Considered Human Research**

If specimens or data were originally collected for non-research purposes AND were added to the repository/database without any identifiers or links to identifiable private information, it is a “non-research” repository/database. Studies using specimens/data from non-research repositories or databases are considered Not Human Subjects Research (NHSR) (Refer to [Section 7.1 - What Is Not Human Subjects Research](#)).

Specimen/data repositories may include two kinds of specimens/data: (1) those collected with the expressed purpose of distribution to other investigators, and (2) those collected by individual investigators with no original intent to share with others, but which are later shared as part of a repository. Any collection which contains specimens/data that are potentially identifiable, either directly or indirectly with a code, and are distributed to

someone other than the named investigator(s) making the collection, regardless of the original intent, is considered to be a repository requiring IRB oversight.

### **Establishing a Repository at USC**

Investigators who collect directly or indirectly identifiable specimens/data require IRB review at the institution of collection (even if different from the site of the repository). Under most circumstances, written informed consent from the subject is required and HIPAA authorization may be required. The informed consent form should include information about the repository and the conditions under which the specimens/data will be shared with others. Some consent forms give participants choices about what types of specimens/data can or cannot be shared.

An investigator may establish a repository for their individual use or with the intention to share the data.

### **Distribution of Specimens/ Data from a USC Biorepository**

Investigators must follow the operating procedures and distribution conditions described in the approved IRB application. These conditions must consider the privacy of the individuals from whom the specimens/data came, the sharing options dictated by participants in the informed consent, and the intent of the person to whom the specimens/data are sent. The recipient of the specimens/data must abide by the conditions specified.

A biorepository committee, established under the IRB guidelines and pursuant to the IRB approval for the repository, should evaluate each request for samples to see if the request is consistent with the IRB's conditions for sharing samples and with the informed consent forms signed by participants. See USC Biorepository Policy  
<http://policy.usc.edu/biorepositories/>

### **Storing Specimens / Data Outside of USC**

If a USC investigator wishes to send specimens/data to a repository located at an external Institution or organization, the investigator must include a copy of the external site's IRB approval letter for operation of the repository in the USC IRB submission.

The IRB at the external site where the repository is located must approve and maintain oversight of a protocol that: (a) specifies the conditions under which data and specimens may be accepted and shared with other researchers and (b) ensures adequate privacy protections for subjects contributing to the repository.

### *Helpful Links*

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- USC Biorepository Policy:  
<http://policy.usc.edu/biorepositories/>
- Research Repositories, Databases, and the HIPAA Privacy Rule  
[https://privacyruleandresearch.nih.gov/research\\_repositories.asp](https://privacyruleandresearch.nih.gov/research_repositories.asp)
- OHRP “Issues to Consider in the Research Use of Stored Data or Tissues”  
<http://www.hhs.gov/ohrp/policy/reposit.html>

## **15.4 NIH Genomic Data Sharing Policy (GDS)**

NIH-funded studies that generate large-scale human genomic data are subject to the [NIH Genomic Data Sharing \(GDS\) Policy](#). According to the GDS Policy, investigators who intend to use research or clinical specimens collected or cell lines created after January 25, 2015, to generate genomic data may only do so with consent, even if the data are generated from specimens that are de-identified. NIH-designated data repositories will not accept genomic data derived from specimens or cell lines collected or created after January 25, 2015, without consent. NIH strongly encourages investigators seeking consent to include consent for future research use and broad sharing of genomic and phenotypic data generated from the specimens or cell lines.

NIH also recognizes that in some circumstances broad sharing may not be consistent with the consent of the research participants whose data are included in the dataset. If the research that involves the generation of genomic and phenotypic data is part of a larger study, such as a clinical trial, and a participant declines to consent to future research use and broad sharing of their data, the participant should not be excluded from the larger study on that basis. If future research use and data sharing are intrinsic to the study, investigators may decline to enroll participants who are unwilling to provide consent for future research use and broad data sharing.



This guidance provides information to be tailored to individual studies and conveyed to prospective participants during the consent process in order to meet GDS Policy expectations. This document will be updated, as appropriate.

### **Guidance for Consent under the GDS Policy**

In order to meet the expectations for future research use and broad sharing under the GDS Policy, the consent should capture and convey in language understandable to prospective participants information along the following lines:

- Genomic and phenotypic data, and any other data relevant for the study (such as exposure or disease status) will be generated and may be used for future research on any topic and shared broadly in a manner consistent with the consent and all applicable federal and state laws and regulations.
- Prior to submitting the data to an NIH-designated data repository, data will be stripped of identifiers such as name, address, account and other identification numbers and will be deidentified by standards consistent with the Common Rule. Safeguards to protect the data according to Federal standards for information protection will be implemented.
- Access to de-identified participant data will be controlled, unless participants explicitly consent to allow unrestricted access to and use of their data for any purpose.
- Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and reidentified data could potentially be used to discriminate against or stigmatize participants, their families, or groups. In addition, there may be unknown risks.
- No direct benefits to participants are expected from any secondary research that may be conducted.
- Participants may withdraw consent for research use of genomic or phenotypic data at any time without penalty or loss of benefits to which the participant is otherwise entitled. In this event, data will be withdrawn from any repository, if possible, but data already distributed for research use will not be retrieved.

- The name and contact information of an individual who is affiliated with the institution and familiar with the research and will be available to address participant questions.

In order to meet the NIH expectations under the GDS Policy, for research projects for which the IRB has granted a waiver of some or all of the required elements of informed consent under 45 CFR 46.116(d), or consent is not required because the activity is not subject to 45 CFR 46, investigators will still need to seek or document consent for future use and broad sharing of genomic and phenotypic data. At minimum, the information described above should be provided to prospective participants. Investigators may request exceptions to the NIH consent expectations for compelling scientific reasons.

Additional guidance for institutions and investigators can be found on the GDS Policy website at <http://grants.nih.gov/grants/gwas/index.htm>

### 15.5 Genetic Research

Genetic information is uniquely personal information. Disclosure of genetic information has the potential to influence employment, insurance, finances, education, family relationships, and possibly self-perception. Therefore, genetic information collected during research must be carefully managed to protect individuals or groups from stigmatization, discrimination, or psychological harm.

Research involving analysis of genetic material can be broadly categorized as genetic testing or genetic research.

Investigators who are conducting genetic research must address the following topics in the iStar application and informed consent form:

- Availability of a geneticist or genetic counselor to counsel participants who receive results of genetic testing
- Participants' rights to opt out of genetic research, to opt out of future research on their genetic specimens, and to request destruction of genetic specimens

### Secondary Subjects in Genetic Research

Family members who are not enrolled as participants but about whom information is collected are called “secondary subjects”. Participants may be asked to describe the age, gender, health information, social history, and relationship of family members. The privacy of these secondary subjects must be protected, even though they are not enrolled as participants. The IRB may require informed consent from secondary subjects or may grant a waiver of informed consent for secondary subjects.

In Genetic research investigators sometimes incidentally learn sensitive information about members of the subject’s family. Subjects and subjects’ family members may or may not want the information known. Investigators conducting genetic research in families must plan ahead for this situation and state whether or not the information will be revealed to participants.

### Human Gene Transfer Research (“Gene Therapy”)

Human gene transfer “gene therapy,” refers to the process of transferring specially engineered genetic material (recombinant DNA or RNA derived from recombinant DNA) into a person. Gene transfer research has additional reviewing, reporting, and consent form requirements because of the high-risk nature of the technology.

At the institutional level, human gene transfer must be reviewed by the IRB and Institutional Biosafety Committee (IBC). For additional information on research involving recombinant DNA, see the [USC IBC website](#). The USC IRB and Biosafety Committee will determine whether individual human gene transfer trials may benefit from review by the NIH Recombinant DNA Advisory Committee (RAC).

### Federal Oversight: FDA, NIH, RAC

#### FDA

The FDA determines whether a sponsor may initiate study of a gene transfer product and, ultimately, whether it is safe and effective for human use. Sponsors of gene transfer products must test their products extensively and meet FDA requirements for safety, purity, and potency before they can be administered to humans or sold in the United States.

#### NIH

Institutions that receive NIH funding must comply with: [NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules](#). NIH Guidelines articulate standards for investigators and Institutions to follow in order to ensure the safe handling and containment of recombinant DNA and products derived from recombinant DNA. \*

#### Recombinant DNA Advisory Committee (RAC)

The Recombinant DNA Advisory Committee is a federal committee that provides recommendations to the NIH Director related to basic and clinical research involving recombinant or synthetic DNA.

Review of individual human gene transfer protocols are limited to cases in which the IBC and or an IRB determine that a protocol would significantly benefit from RAC review and meets one or more of the following criteria:

- 1) The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting unknown risks;
- 2) The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or
- 3) The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies involved in the review at an initial site(s) to evaluate the protocol rigorously.

- [NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules](#)

## **15.6 Pregnancy Testing in Research**

All females who are of child-bearing potential being considered for participation in a research study, in which there is a possibility of harm to a fetus from the study interventions, must have a negative pregnancy test before undergoing any study-related activities with a potential risk to a fetus. Protocols where the study interventions themselves do not pose a potential risk to a fetus, even if the interventions the individual may undergo for routine or standard care are greater than minimal risk, (for example, a study where the intervention was the collection of blood samples following surgery that is part of the individual's routine care) would not require pregnancy testing or the use of contraception.

Although in most cases exclusion of pregnant women from research studies is justifiable based on uncertainty about fetal risks or on the potential effect of the physiological changes accompanying pregnancy on measures and outcomes of interest, there may be circumstances where the potential benefits to mother and/or fetus outweigh the risks—for example, in the case of a potentially life-threatening condition in the mother that poses a greater risk to a fetus than study interventions. Such cases must be considered by a convened IRB with appropriate expertise present prior to the onset of any study activities.

## **15.7 Research Involving HIV Testing and AIDS**

Confidentiality is the most sensitive aspect of AIDS research from the perspective of the rights and welfare of the subjects. Improper disclosure could have severe consequences for research participants, by threatening family relationships, job security, employability, or ability to obtain credit or insurance. In light of these risks, special precautions should be taken to preserve confidentiality. Limits to confidentiality should be carefully explained to potential subjects so they can make fully informed decision about participating.

The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take into account the possibility of a review of records by the funding agency and by FDA officials if the research is subject to FDA

regulations [21 CFR 50](#). The informed consent form must disclose that positive HIV tests will be reported to public health agencies.

### California Law and HIV Research

The California Health and Safety Code ([Section 121075-121125](#)) provides additional protections for research records in studies relating to HIV or AIDS.

“Confidential research records” includes any data in a personally identifying form (such as name, social security number, address, employer or other information that could, directly or indirectly, lead to the identification of the individual research subject) developed or acquired by any person in the course of conducting research relating to AIDS.

Confidential research records developed or acquired by any person in the course of conducting research, or a research study relating to AIDS, shall be confidential and shall not be disclosed by any person in possession of the research record, nor shall these records be discoverable, nor shall any person produce any confidential research record except in the following situations:

- Confidential research records may be disclosed in accordance with the prior written consent of the research subject to whom the confidential research records relate, but only to the extent, under the circumstances, to the persons and for the purposes the written consent authorizes. Any disclosure made pursuant to such prior written consent shall contain the following statement:

*This information has been disclosed to you from a confidential research record the confidentiality of which is protected by state law and any further disclosure of it without specific prior written consent of the person to whom it pertains is prohibited. Violation of these confidentiality guarantees may subject you to civil or criminal liabilities.*

- Confidential research records may be disclosed without prior written consent to:
  - Medical personnel for a medical emergency, as relevant
  - The California Department of Health Services for the conduct of a special

The content of any confidential research record shall be disclosed to the research subject, the legal representative of the research subject if the research subject is a minor, or the

personal representative of a deceased research subject to whom the record pertains within 30 days after a written request is made for such records by the research subject or the legal representative.

For additional information on California laws, please refer to “A Brief Guide to California's HIV-AIDS Laws” at

[http://www.cdph.ca.gov/programs/aids/Documents/RPT2010\\_01HIVAIDSLaws2009.pdf](http://www.cdph.ca.gov/programs/aids/Documents/RPT2010_01HIVAIDSLaws2009.pdf)

### **Policy on Informing Subjects about HIV Serostatus**

It is the policy of the IRB, as required by the Public Health Service (PHS), that when HIV testing is conducted as part of a research project, individuals whose test results are associated with personal identifiers must be informed of their test results and be provided with the opportunity to receive appropriate counseling. Individuals may not be given the option to "not know" the results, either at the time of consenting to be tested or thereafter. This policy does not apply to testing situations in which subjects consent to be tested and where results cannot be linked to individual subjects by anyone other than the subjects themselves.

### **Counseling**

Any person tested for HIV infection should receive the results of their tests and counseling in a timely fashion from an individual qualified to provide test counseling and partner notification services.

### **Exceptions to Informing Subjects about HIV Serostatus**

- **Individual Subjects**

When there are compelling and immediate reasons that justify not informing an individual of their positive HIV test results - the details of the exception shall be documented by the responsible individual(s). The investigator must promptly report the exception to the IRB without identifying the individual.

- **Protocol Design**

An exception to informing subjects of their test results may be permitted with the advance approval of the IRB.

## Chapter 16: Student Research

### Chapter Contents

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- 16.2 – Classroom Assignments Involving Human Subjects
- 16.3 – Requirements of Faculty Who Supervise Student Research
- 16.4 – IRB Student Mentor
- 16.5 – International Research Conducted by Students
- 16.6 – Students as Research Subjects
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- 16.8 – Student Subject Pools



# Chapter 16

## Student Research

This chapter describes the responsibilities of faculty advisors and students who conduct human subjects research. Additionally, other topics specific to student research are discussed including assistance provided by the IRB Student Mentor, international research considerations, mandatory reporting responsibilities, and subject pool policies.

### 16.1 Introduction to Student Research

In accordance with federal regulations, the IRB requires that all human subjects' research be prospectively reviewed by an IRB including master's theses, doctoral dissertations, and all student research projects involving human subjects. Under IRB policy, no UPC student research will be approved with a study design that includes administration of medications. For unique situations, this prohibition may be discussed with the IRB.

### 16.2 Classroom Assignments Involving Human Subjects

The University recognizes that some student projects are conducted to fulfill course requirements, and involve activities that might appear to be human subjects research. Classroom assignments **do not** require IRB approval. These projects typically fulfill a course requirement, are often completed in one semester, and are designed to teach research methods. Faculty members design these assignments to engage students in interaction with individuals, gather data about individuals, and/or illustrate concepts covered in the course. For the most part, they are not intended to create new knowledge or to lead to scholarly publication. The publication of classroom study results or poster sessions at a professional meeting does not make the project human subjects research. These classroom assignments do not meet the federal definition of [human subjects research](#). Additionally, library research or content analysis of public documents is **not** human subjects research. If students or faculty are uncertain if a classroom project must be reviewed by the IRB, they should contact the IRB.

For projects that do not require IRB review, faculty may direct students to a practice IRB application through the iStar [Sandbox](#) Training application. This site allows students to familiarize themselves with iStar, the online application used for IRB submissions, and work on mock IRB submissions.

Additionally, it is recommended that students working on classroom projects complete the **Human Subjects Training** course available online at Collaborative IRB Training Initiative ([CITI](#)). This training is **not optional** for projects required to undergo IRB review.

At USC, students involved in classroom assignments are encouraged to follow the University's Code of Ethics and policies when designing and conducting projects with human volunteers.

Faculty members assigning projects in research methods classes are expected to help students understand ethical obligations toward anyone with whom they interact to complete their assignments.

### 16.3 Requirements of Faculty Who Supervise Student Research

Faculty should determine whether an assigned project involving human subjects is defined as a course-related student project. Faculty is strongly encouraged to contact the IRB office for assistance in making this determination and for education on how to mentor students through the IRB and human subjects research process. Faculty should discuss general principles of research ethics with the class prior to the initiation of any project involving human subjects. It may be possible to bundle similar studies conducted under one faculty advisor, decreasing the number of submissions that need to be submitted to the IRB (please contact the IRB for further information). No IRB approval may be given after a classroom-assigned study is begun or completed.

### Faculty Responsibilities for the Protection of Human Subjects

Faculty who supervise student research are responsible for the protection of human subjects and are required to:

- Determine whether projects require IRB review and assist students with the process.
- Discuss research ethics with the students.
- Familiarize themselves and students with ethical and regulatory mandates for human subjects research
- Approving the student's IRB application and signing a Faculty Advisor Assurance outlining their responsibilities.
- Monitor student projects focusing on maintaining confidentiality, privacy, the level of risk, voluntary participation and withdrawal, and informed consent.
- Assure prompt reporting to the IRB of any event that requires reporting in accordance with the IRB policies and procedures for Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (refer to [Section 20.2 – Unanticipated Problems Involving Risks to Subjects or Others](#)).
- Complete CITI (On-line human subject protection training)

### 16.4 IRB Student Mentor

The IRB student mentor is a graduate assistant at the Office for the Protection of Research Subjects (OPRS). The IRB student mentor, like other graduate assistants at USC, contributes to the research and teaching activities of the University while pursuing academic degrees.

As a peer mentor, the IRB student mentor counsels USC student investigators on issues related to human subjects protection and the IRB application process through individual advising and group workshops. The IRB student mentor also works closely with the Executive Director of OPRS, and individual schools and departments on the University Park campus to continuously plan and implement outreach programs for the USC community. These programs educate faculty, students, and staff on important issues pertaining to human subjects protection in research activities.

The IRB student mentor serves as a liaison between USC students and OPRS, through whom OPRS develops a better understanding of students' needs and concerns as they relate to protecting research subjects.

For more information visit <https://oprs.usc.edu/about/#studentmentor>

### 16.5 International Research Conducted by Students

**The following policy is specific to international research conducted by USC students and is not applicable to funded clinical trials.**

International research involves projects that are conducted outside of the United States. Federal regulations acknowledge that local customs, norms, and laws where the research will take place may differ from U.S. regulations governing research. Funded student research is required to meet U.S. standards wherever it is conducted. For unfunded student research, USC IRBs may accept comparable standards depending on the risk level. It is the expectation that there will be a local contact and/or consultant for the student researcher who will provide information on local laws and cultural norms.

#### IRB Considerations

If an unfunded study involves less than minimal risk to participants, domestic IRB approval may be sufficient. Examples include surveys that compare use of social media in U.S. adults versus adults in another country or other questionnaires that do not collect sensitive information. Students and/or faculty should contact the IRB for additional information.

If a study involves more than minimal risk to participants, USC requires protocol review and approval by an outside IRB/Ethical Review Committee (EC), equivalent organization in the country where the research will occur (refer to [7.11](#) – International Research). Examples of these studies include surveys about high-risk behavior or questionnaires that ask questions about HIV status.

International studies will follow the same criteria for IRB review and approval as domestic studies. For example, a less than minimal risk study can receive an expedited review, whether the study is conducted within the US or abroad.

Research policies for studies conducted within the U.S. apply to international research wherever possible. In addition, international research protocols often include:

- Explanations of cultural differences that influenced the study design and the consent process

- Rationale for conducting the study with an international population
- Information regarding the host country's IRB, Ethical Review Committee or equivalent organization and documentation of its approval of the research, if applicable
- A copy of the letter(s) of agreement on letterhead stationery with signatures from the local host Institution(s), and from government officials, as necessary, to cooperate in the proposed research
- A copy of the informed consent form, if used, in English, and a copy in the appropriate native language(s)
- Information regarding the literacy level of the expected subjects and how this may affect the informed consent process
- A description of the informed consent process, including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects
- A description of the processes for assuring anonymity and/or confidentiality of all data, and a description of the methods of transport and security of data to the United States, if applicable
- If data will be collected by someone other than the researcher, the curriculum vitae of the individual and letters of agreement should be included on letterhead stationery and with original signatures from the research collaborators
- If compensation is to be given to subjects, justification for the amount of money or goods should be provided and an explanation as to how this compensation is proportionate to the average annual income of people in the host country should be examined

### Faculty Advisor Responsibilities

Faculty Advisors are expected to remain in contact with students conducting research at any foreign site to ensure safety and welfare of the participants and student. Faculty must also prepare students for cultural differences they will encounter in an international setting. Faculty who supervise student researchers must be aware of their responsibilities

and their role in the protection of human subjects. Refer to [Section 16.3 – Requirements of Faculty Who Supervise Student Research](#) for more information.

### 16.6 Students as Research Subjects

Consistent with an overall concern that no research subject should be coerced, researchers must take precautions to avoid the unintentional or subliminal coercion that can occur when potential research subjects are also students. For this reason, researchers should avoid using their own students as research subjects. Researchers who wish to use their own students must be able to provide a good scientific reason, rather than convenience, for selecting their own students as research subjects.

In instances where investigators can provide justification for using their own students in their research, the IRB generally requires that someone other than the investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor, whether or not a student participated in the research project until after final grades have been determined. The students should be informed of these procedures in the informed consent form. In addition, it is generally recommended that the investigator/professor provide a recruitment flyer or letter to the students, so that the students may be the initiators and contact the investigator/professor regarding the research study.

### 16.7 Student Researchers' Abuse Reporting Obligations

Mandated reporters are individuals who are obligated by law to report suspected cases of child and/or elder abuse and neglect. In general, any person who has contact with children or the elderly in a professional capacity is a mandated reporter, although laws vary from state to state, as does the legal entity to which reports must be made. For the California Penal Code definition of mandated reporter see [Elder Abuse and Dependent Adult Civil Protection Act Section 15630 \(a\)](#) and Child Abuse and Neglect Reporting Act Section [11165.7](#). USC policies and procedures covering “mandated reporter” and the reporting of abuse/neglect can be found at the following site: <http://policy.usc.edu/mandated-reporters/>.

### Student Researchers' Abuse Reporting Obligations

Although child or elder abuse may be disclosed or suspected in many research disciplines, research conducted in certain schools or departments (gerontology, psychology and social work) often provide situations in which evidence or disclosure of such abuse is more likely to be encountered. In the event that a student researcher becomes aware of, or reasonably suspects, that a study subject has been the victim of child or elder abuse, the student should follow these procedures:

If student researcher's faculty advisor is a mandated reporter, the student researcher should notify that mandated reporter of the suspected abuse. A mandated reporter is legally obligated to follow up.

Even when the student's faculty advisor is *not* a mandated reporter, the student researcher should notify the faculty advisor and/or the department of their concerns.

If one is not a mandated reporter, he or she need not make a mandated report however, students have an ethical obligation to report their suspicion to a faculty member for further action.

### Abuse Disclosure Notification in Consent Documents

Disclosing the obligation to report certain types of neglect and abuse in the informed consent process is required for research projects involving mandated reporters. However, even though the requirement to report only applies to mandated reporters, [Section 11166.05](#) broadens the scope of possible reporting beyond the mandated areas by allowing (not requiring) mandated reporters to make reports regarding children suffering from "serious emotional damage or... at a substantial risk of suffering serious emotional damage, evidenced by states of being or behavior, including, but not limited to, severe anxiety, depression, withdrawal, or untoward aggressive behavior toward self or others". This should be addressed in the informed consent process.

### 16.8 Student Subject Pools

A Subject Pool is a research resource used by some departments and schools in academic settings to enroll a large number of “available” subjects as potential volunteers. These volunteers are used in studies for that school or department. Subject Pools serve several roles: to provide researchers a pool from which to recruit primarily student participants for their studies and to familiarize students with the research process as subjects and researchers.

Participants in subject pools may be compensated for their time through course credit, extra credit or other means. These uses make subject pools commonplace in Social and Behavioral Studies.

**Note:** students must be provided an alternative to participation in the subject pool. The alternative assignment must not coerce subjects to participate in the subject pool. To prevent undue influence, the assignment should require approximately the same commitment of time and effort to complete as would participation in the subject pool.

#### Extra Credit

The IRB can approve projects that give extra credit to student subjects for participating in a research project only when alternative means of obtaining equivalent extra credit with an equivalent effort is available for students who decide not to participate in the research. The IRB carefully reviews the alternatives to participation to ensure that students are not being coerced.

The informed consent form should detail the consequences of withdrawing from a project prior to completing the research activities (extra credit should be given despite withdrawal). In general, the IRB favors giving extra credit even if a subject withdraws, unless the student withdraws immediately or there is clear evidence of bad faith on the part of the student.

#### Marshall School of Business Subject Pools

The Marshall School of Business has an unpaid student subject pool conducted by the Department of Management and Organization and a paid subject pool open to the general public conducted by the Department of Marketing. Links to the Marshall School subject pools and to additional information from Marshall are listed below.



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- Policy for Behavioral Studies at Marshall School of Business  
<http://www.uscresearch.org/poolinfo.php>
- Department of Management and Organization Consent Procedures  
<http://www.uscresearch.org/consentprocedures.html>
- Department of Management and Organization Subject Pool Access  
<https://marshall-mor.sona-systems.com/Default.aspx?ReturnUrl=/>
- Department of Marketing Consent Procedures  
<http://www.uscresearch.org/mktconsentprocedures.html>
- Department of Marketing Paid Subject Pool Access  
<https://marshall-research.sona-systems.com/Default.aspx?ReturnUrl=/>

### Department of Psychology Subject Pool

The Department of Psychology subject pool is only open to USC students. To access the Psychology Subject Pool Webpage, click on link below.

- Department of Psychology Subject Pool Webpage  
<https://dornsife.usc.edu/psyc/research-subject-pool/>

### Recent Federal Guidance on Subject Pool and Penalties for “No Shows”

#### Penalties for no-shows may not be assessed in subject pools

The Office for Human Research Protections (OHRP) posted on its website a letter stating that imposing penalty credits on students who fail to show up for scheduled appointments with investigators without canceling by a specified deadline violates the requirement of Department of Health and Human Services (DHHS) regulation 45 CFR part 46.116(a)(8). The letter can be viewed by clicking [here](#). At USC, the OHRP position is upheld for all research and no such penalty credits may be imposed on subject pool participants.

Correspondence with OHRP has indicated that in subject pool policies, penalties may be assessed when students:

- Sign up for a study for which they are not eligible

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- Sign up for the same study for multiple different times
- Sign up for a study in which they have already participate

	<p>Chapter 17:</p> <p><b>Special Research Topics</b></p>
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<p>17.1 – Secondary Data Analysis</p> <p>17.2 – Survey Research</p> <p>17.3 – Internet Research</p> <p>17.4 – Incidental Findings in Research</p> <p>17.5 – Difference Between Human Subjects Research and Quality Improvement Research</p> <p>17.6 – Institutional Research</p> <p>17.7 – Oral History Research</p> <p>17.8 – Pilot Studies</p> <p>17.9 – Research Using Deception</p>	

# Chapter 17

## Special Research Topics

This chapter focuses on special research topics. Some topics discussed in this chapter are not subject to IRB review, other topics that are of misconstrued as human subjects research.

### 17.1 Secondary Data Analysis

Any research that involves secondary use of data where individual identifiable subject records are involved requires IRB review. For example, an investigator who plans to analyze an existing data set obtained from another source should submit an application for IRB review if the data set contains records on individual human subjects. If the data set contains no identifiers (either direct or linked code numbers), the project is not human subjects research (refer to [Section 7.1 - Human Subjects Research: What is and What is Not](#) for definitions of “human subject”).

If the data set contains identifiers, and does not contain private information, the project is not human subjects research. Otherwise, the project may be eligible for expedited review. The IRB may waive informed consent if research is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

### 17.2 Survey Research

Survey research is a research method that obtains data through the use of surveys, questionnaires, interviews, and focus groups. Because of the methodology, it is often assumed that all survey research is minimal risk. However, survey research may involve greater than minimal risk. For example, a survey or interview that asks questions about sensitive topics (childhood abuse, sexual functioning, immigration status) are not minimal risk. These questions may cause emotional stress, discomfort, or may have legal or social implications, and therefore may require full IRB review.

The term anonymous is sometimes confused with the term confidential. In human subjects research, anonymous means that there is no link or identifier to the subject. If a link exists elsewhere, but is not available to the researcher, the IRB must determine the category of risk, and/or difficulty of discovery of the subject's identity, the IRB cannot consider the information anonymous.

Survey research may be classified as exempt from the regulations if the information obtained is recorded in a way that the subject cannot be identified (either directly or through a code number or link), in other words, if the research data is anonymous.

A survey or interview study may also be considered exempt from the regulations even when the data is not anonymous if the information being gathered could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

If a study is not anonymous and contains information that, if known, could be damaging as described above, but it does not rise to the level of more than minimal risk, it may be given expedited approval. Although the IRB application gives the investigator the opportunity to indicate a classification, the IRB makes the final determination as to the classification of exempt or expedited.

For minimal risk surveys (mail-out or web-based), it may be appropriate to request the IRB to waive the requirement for the subject's signature on an informed consent form. When the subject's signature requirement is waived, generally the investigator provides all of the required elements of consent in an Information Sheet, with a statement that returning the survey or questionnaire will constitute voluntary agreement/consent to participate in the research study. For additional information, refer to [Section 10.10 – Waivers of Informed Consent](#).

If survey research is supported by or conducted in collaboration with the Department of Defense (DOD), follow DOD requirements for additional review (refer to [Section 3.2 - Research Supported by the Department of Defense](#)).

### 17.3 Internet Research

Human subjects research that is designed to recruit participants or collect data through the internet must be reviewed by the USC IRB. Research activities taking place on the

Internet are subject to, and will be evaluated based on the same standards (45 CFR 46.111) that govern all research involving human subjects.

Conducting research using the internet includes both use of the web as a tool for research, and use of the web as a locale, venue, or subject of research. These tools include social platforms such as Facebook, Twitter, Skype, YouTube, and data capture sites such as Amazon Mechanical Turk and Quintiles. All accessible with smart phones, tablets and laptops.

### Primary Requirements for Internet Data Collection

Web-based data collection methods may include the use of existing data, observations, remote measurement tracking, interventions, and survey/interview procedures.

In order to receive IRB approval, the researcher must demonstrate that the following considerations have been met:

- Risks to participants are minimized, and are reasonable in relation to anticipated benefits;
- that selection of participants is equitable;
- Informed consent will be sought from each participant and appropriately documented;
- Participant data will be collected to protect participant privacy, monitored as needed to ensure participant safety, and maintained in a manner that protects participant confidentiality; and
- The investigator will comply with applicable terms of agreement set forth by the platform being used for research.

### Protocol Design and Internet Research

Online research and the use of social media presents considerations that the researcher must address in the IRB application:

#### Recruitment

The identification and contact of potential research participants is possible through

various social media platforms and surveys. Online recruitment takes place in many forms. Examples include websites devoted to clinical trial, electronic flyers posted on social media site, posts to online forums, blogs and group discussion boards.

Locally produced recruitment material that does not meet exempt review criteria, must be submitted to the IRB for review and approval. This includes text of the recruitment script, and the context in which the recruitment takes place (posting a message on a newsgroup, mass e-mailings, or websites created for recruitment of participants).

### **Informed Consent**

An internet consent should include all the elements of the regular signed consent. The consent line should read, “By completing the survey you are agreeing to participate in the research”. Internet-based surveys should include “I agree” or “I do not agree” buttons on the website for participants to click their choice of whether they consent to participate or not. The participant must *prospectively* be informed of and consent to any contact via social media or other electronic forum. If all study procedures are taking place online, signed written consent may not be possible (unless an electronic signature process is used), so the researcher can request a waiver of documentation of consent at the time of IRB review. The signature lines can be replaced with a checkbox, and participants can indicate their consent by checking a box or clicking forward from the consent document.

If the IRB approves research and requires documented consent and the PI does not plan to maintain the anonymity of participants, the researcher may email the consent form to participants who may type their name and date into the spaces provided on the consent form and return it to the researcher via email.

### **Participant privacy**

Is the online site where the research is being conducted considered a public space (i.e. Twitter) or a private space (i.e. password protected forums)? Research utilizing data that are both existing and public is not considered human subjects research and does not require IRB review. Data accessible only through special permission are generally not considered public. However, if steps are required to access data (e.g., registration/login, payment, etc.) but access is not restricted beyond these steps (e.g., anyone who creates a username and password can access the data) the data may qualify as publicly available. When determining whether data are public, the investigator must decide if there exists an expectation of privacy. If it is determined that the data were not intended for public use, even if the data are technically available to the public, the data should be considered

private. Researchers accessing data that are identifiable or that when combined could readily be identifiable must obtain IRB review and approval.

### **Data confidentiality and security**

Data being collected through the internet should be in an encrypted format to ensure that any data intercepted during transmission cannot be decoded and individual responses cannot be traced to an individual respondent. All databases storing sensitive and identifiable information must be protected, regardless of whether they are created and maintained by commercial firms or by individuals. Participants should completely log off the computer when finished to help maintain privacy.

Researchers are cautioned that encryption standards vary from country to country and that there are legal restrictions regarding the export of certain encryption software outside US boundaries. The investigator is responsible for assuring the security and privacy policies of the vendor are consistent with the [USC Information Security Policy](#).

### **Sample integrity**

How will the researcher ensure they are accessing their target population? (Participants may check various boxes to indicate that they meet the inclusion criteria, the researchers will not be able to confirm the validity of this information) Researchers conducting research which excludes minor participants should describe the procedures to be employed to authenticate that the participants are adults. Age is difficult to verify on the Internet. To exclude minors, the researcher may state the minimum age of participants on a web page, information sheet, and/or consent document at the outset of the study. Individuals should be able to press a “not eligible, please discontinue” button (give the location) if they are not yet 18 years old, or an “I agree to participate and certify that I am 18 years of age or older” button.

### **Participant Withdrawal**

How will the researcher handle the data of participants who want to drop out of the study? Whether or not the data can be destroyed if a participant decides to withdraw should be indicated in the consent; if the data were collected anonymously, the researcher may not be able to identify the participant’s data to destroy it.

### **Compensation**



When providing compensation, the following are recommended to maintain anonymity:

- electronic gift cards or certificates sent via email
- cash/gift card sent through the postal service (note: using the subject's mailing address prohibits research being anonymous)
- do not link compensation to contact information

### Minors in Internet Research

Researchers working with children online are also subject to the Children's Online Privacy Protection Act (COPPA). *COPPA prohibits researchers from collecting personal information from a child without posting notices about how the information will be used and without getting verifiable parental consent.*

[More information on COPPA and Children's Privacy can be found on the FTC website.](#)

If the study involves minimal risk, assent and/or parental permission can be waived. The IRB may require the use of information sheets when child assent and/or parental permission are waived. The researcher must provide a plan for obtaining parental permission when applicable though verification may be difficult.

### Online Surveys

Survey research is one of the most common forms of web-based research.

Researchers are advised to format survey instruments in a way that will allow subjects to refuse to answer specific questions. For example, the list of responses can include an option such as "Decline to answer." In addition, subjects must always be given the option to withdraw from a study, even while in the middle of a survey.

Investigators should review confidentiality measures and data security policies for the given online survey tool and make sure that they are described in the protocol. When using an online anonymous survey, the researchers should ask the vendor to withhold the IP addresses of the participants. If security measures are not in line with what the IRB requires, use of the given survey tool may not be approved. Research subjects also need to be informed of data security measures.

Researchers and the IRB should have a familiarity with the survey software being used, the types of information being collected (e.g., IP address, email address), the options the survey software offers regarding what information to collect, the ways in which information will be stored, and how any identifying information will be de-linked from survey data. For assistance, contact the USC Office of the Chief Information Security Officer at <https://itservices.usc.edu/security/>

USC provides REDCap (Research Electronic Data Capture): a secure web application for building and managing online surveys and databases. Visit USC Information Technology Services – [Research Software](#).

### Chatrooms and Private Forums

Private forums, communities, and chatrooms are examples of locations on the internet that limit access and view to registered members only. Site administrators and moderators control admission and content that cannot be viewed by the general public. Members expect their comments and interactions to remain private. Researchers who wish to collect data should be transparent regarding their role in interactions with these groups. Investigators must obtain an affirmative opt-in prior to using members content to conduct research. And seek explicit permission from members to quote their comments.

## 17.4 Incidental Findings in Research

Incidental Findings in research are results obtained/uncovered about an individual research subject, for which there is a potential health importance but is **beyond the aims of the study**. It may arise in collecting or analyzing research data/images or part of establishing eligibility or for purposes of the study itself (samples, eligibility, screening).

The research proposal should delineate how incidental findings will be managed in the research. The informed consent should be consistent with this plan. In general, it is contemplated that the health care provider/investigator will disclose the relevant information and ensure appropriate referral or care are recommended or provided.

### Recommendations for Incidental Findings

- Researchers should develop a plan to manage anticipated incidental findings, including but not limited to those findings known to be significant and clinically

actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by an Institutional Review Board.

- Researchers should develop a process for evaluating and managing unanticipated findings. Researchers who discover an unanticipated incidental finding of concern should assess its significance, consulting with experts as appropriate.

### **USC Dornsife Imaging Center (DNI) Policy and process for handling Incidental Findings**

The Dornsife Imaging Center (DNI) is a research facility that is part of the College of Letters, Arts & Sciences and is **not** affiliated with the Keck School of Medicine or the University Hospital.

This DNI policy does not apply to biomedical researchers who conduct research at HSC. They are subject to additional internal policies established by their home division/department.

Researchers using or planning to use DNI services must familiarize themselves with the Dornsife Imaging Center policies. The policies are accessible online:

<http://dornsifecms.usc.edu/brainimaging/policies/>

The policy includes mandatory informed consent language, consent for neuroimaging consult, subject eligibility. PI and research staff adherence to policy.

### **17.5 Difference Between Human Subjects Research and Quality Improvement Research**

The term “quality improvement” is the process of reviewing, analyzing, or evaluating patient and/or provider data that may indicate (the need for) changes in systems or procedures that would improve the quality of care.

The distinction between quality improvement and human subjects research is intent. When an activity is specifically initiated with a goal of evaluating and possibly improving the performance of institutional practice in relation to an established standard, the activity is called quality improvement.

If a project is originally initiated as a quality improvement project but the findings may be of interest beyond the institution, publishing the findings does not make it human subjects research. When there are mixed aims involving quality improvement activities and research, IRB review is required. If the individual who conducted a quality improvement project chooses to expand the findings into a research study, IRB review is required at that time.

In order to distinguish research from quality improvement, use the following criteria:

- Intent- the purpose/aim statement should be clear. In general, quality improvement projects are aimed at improving local systems of care (nongeneralizable). If the intent is to promote “betterment” of a process of care or a clinical outcome, then the project is quality improvement.

If any of the following criteria are met, the study may require IRB review:

- if the primary intent of the study is to generate generalizable results
- if the study will impose risks or burdens on the subject/patient beyond the standard of practice it may be human subjects research
- if a study involves randomization or procedures that may be considered not standard of care

### 17.6 Institutional Research

Institutional is research conducted for internal use , or to evaluate programs or to inform management practice and decision-making, falls outside the federal definition [\[45 Part 46\]](#) of “research” or “human subjects” and therefore does not need to undergo review by the IRB.

Institutional research involves data collection, analysis, or reporting about educational, administrative, or other aspects of a college or university for either institutional self-improvement or external reporting. In most universities, institutional research informs such issues as enrollment management; program evaluation; student outcomes assessment; space planning and utilization; financial analysis; and faculty or staff planning. Data most often include institutional databases, surveys, focus groups, interviews, tests, work samples, and archival materials.

While the term “institutional research” is most often used in an academic setting, the function is found in a wide array of educational, service, and other organizations. Many health care providers and service organizations have offices of Quality Assurance, Organizational Effectiveness, Planning and Assessment, or Evaluation.

### 17.7 Oral History Research

Oral history is not considered research as defined by the U.S. Department of Health and Human Services (DHHS) regulations. The DHHS Office for Human Research Protection does not consider oral history to meet the regulatory definition of “research” and therefore is excluded entirely from IRB review, without seeking formal exemption. If oral history projects **do not meet** the regulatory definition of research they do not require IRB review. However, oral historians are encouraged to consult the IRB if they have questions.

### 17.8 Pilot Studies

Pilot studies must be submitted for IRB review and approval. IRB submissions should be identified as pilot studies. This helps the committee to contextualize the research, particularly when it comes to justification for the sample size and/or research design.

Data from pilot studies is used to refine and support the expansion of a protocol that will be submitted for future IRB review and approval. Data from pilot studies may be saved for later inclusion with data from an IRB approved pilot study.

#### Pilot Testing

Pilot testing most commonly refers to the process of evaluating the usefulness or credibility of a test instruments to be used in a research study. The information collected in pilot testing assists in refining instruments, surveys and data collection procedures. This aids in minimizing instrument error and development of more precise research design. Pilot testing to validate questionnaires, surveys and instruments as described above does not constitute a pilot study and does not require IRB approval.

## **17.9 Research Using Deception**

Deception is a technique that may be used in some research despite a general ethical concern about fully informed consent. For certain kinds of less than fully informed consent, exceptions to this prohibition are allowed primarily because there is not expectation of harm that will result. Examples of deception include studies in which the investigator does not disclose the true purpose of the research to subjects, does not explain the ultimate use of the subjects' data, or uses a "confederate" acting on behalf of the study team, unbeknownst to the subject. Studies using deception routinely receive expedited or Full Board review when the conditions of deception would be problematic for the subjects and pose risk of physical or emotional stress. For these studies, there should be a prompt and complete debriefing of the subjects. A debriefing statement for IRB review should be submitted along with the informed consent form. Debriefing may include explaining the research, and if possible, providing the opportunity for withdrawal of personal responses or withdrawal from participation in the study.

### **Deception Qualifying for Exempt Review**

The following pertains to the use of deception in research that qualifies for exempt review:

- The omission of minor facts is not equivalent to deception.
- Exempt studies using deception in surveys/games/focus groups where the deception is of no risk can receive the Exempt determination.
- Psychological research often justifies a need for use of deception to reduce biased responses that subjects may feel will reflect poorly on them. Study findings suggest that such deception is not harmful to subjects.

## Chapter 18: FDA-Regulated Research

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# Chapter 18

## FDA-Regulated Research

This chapter covers research involving products regulated by the Food and Drug Administration (FDA), including investigational and approved drugs, biologics, and devices. This chapter also describes procedures for emergency use of investigational drugs, biologics, and devices, and other regulations unique to FDA-regulated products. Research involving FDA-regulated products may also be subject to [45 CFR 46](#), California regulations, and institutional policies.

### 18.1 FDA-Regulated Research

The FDA regulations for drugs are outlined in [21 CFR 312](#), devices are in [21 CFR 812](#), and biologics are in [21 CFR 600](#). FDA regulations for informed consent (21 CFR 50) and Institutional Review Boards (21 CFR 56) also apply. For a comparison of FDA and HHS regulations on human subject protection, click [here](#). Reporting of adverse events and unanticipated problems related to research on FDA-regulated products is covered in [Chapter 20 - Reportable Events, Noncompliance, Suspensions, and Terminations](#).

The USC IRBs are registered with both the Office for Human Research Protections (OHRP) and FDA in the OHRP database.

#### *Definitions for FDA Regulated Research*

<b>Biological Product</b>	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings.
<b>Clinical Investigation</b>	Any experiment that involves a test article and one or more human subjects.



<b>Device</b>	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body; AND which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.
<b>Drug</b>	Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body.
<b>Test Article</b>	Any drug, biological product, medical device, electronic product, or other product regulated by the FDA.

### 18.2 Investigational Drugs

An Investigational New Drug (IND) application is the FDA regulatory mechanism by which a sponsor can ship an unapproved drug or biologic to study sites and initiate clinical research on the drug. The FDA assigns an IND number and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk. An IND application is required for:

- Testing of unapproved drugs
- Testing of approved drugs that involves new indications or significant labeling changes

IND regulations are found at [21 CFR 312](#).

Investigators must describe the regulatory status of each study drug in the iStar application as well as rationale for determining whether or not an IND is required for the study. If a drug is covered by an IND, the IND number and documentation of the IND number must be provided. Documentation may include FDA correspondence to the sponsor that provides the IND number, or a clinical protocol or investigator's brochure that identifies the IND number. The IRB staff verifies that there is an IND number and

## Chapter 18: FDA-Regulated Research

that the number provided in the iStar application is correct. The study will not be approved until the IND number is verified.

Certain drug investigations may be exempt from the requirement for an IND. A clinical investigation of a **marketed** drug is exempt from the IND requirements if **all** of the criteria are met:

- The drug product is lawfully marketed in the United States
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR 56) and with the requirements for informed consent (21 CFR 50)
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (the investigation is not intended to promote or commercialize the drug product)

Investigations of marketed drugs or biologics must have an IND if none of the exemptions described above apply. When the principal intent of the investigation is to develop information about an approved product's safety or efficacy, IRB approval and an IND are required.

Additional information about exemptions from IND requirements is found in the FDA guidance document [“Investigational New Drug Applications \(INDs\) - Determining Whether Human Research Studies Can Be Conducted Without an IND.”](#)

The IRB will determine if the IND exemption proposed in the iStar application is consistent with FDA regulations and guidance. The committee determination will be recorded in the meeting minutes. If there is no IND and the study does not meet any of the FDA exemption categories, the IRB will not approve the study. The investigator may

re-submit the iStar application after obtaining an IND number from the FDA or obtaining a written determination from the FDA that no IND is needed.

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires an IND, the investigator should contact the FDA directly for a determination. The IRB may require that an investigator contact the FDA if this has not been done at the time of IRB review. If the FDA indicates that an IND is not required, documentation of contact with the FDA is required. This may be either a written notification from the FDA, or documentation of contact with the FDA, including who was contacted, the phone number, the time of the call, and a summary of the information provided by the FDA.

### Off-Label Use

An IND is not required when a health care provider prescribes a marketed drug to treat an individual patient for an unlabeled indication. This is referred to as “off-label”, meaning the treatment is being used in a manner not specified in the FDA’s approved packaging label or insert. An IND is not required because this use falls within the scope of medical practice and it is not research.

### Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, investigational products may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, life-threatening, or debilitating condition, the FDA has a mechanism that allows expanded access to investigational drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from investigational drugs that have potential benefits.

Expanded access to investigational drugs requires an IND and prospective IRB approval. In some cases, the sponsor will have an expanded access protocol under an existing IND. In other cases, an investigator may have to obtain a new IND for expanded access to an investigational drug. A new IND is needed if there is no existing IND or if the sponsor does not want to amend an existing IND to include expanded access. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

### Individual Expanded Access Involving Investigational New Drugs

Individual Expanded Access allows physicians access to investigational drugs and biologics for the treatment of a single patient ([21 CFR 56.111](#)). The [Individual Patient Expanded Access Investigational New Drug Application](#) - Form FDA 3926, may be completed to request access to investigational treatments for patients when there is no other option to treat their serious disease or condition. Still available for use are Form 1571 and Form 1572 for single patient expanded access submissions; however, Form 3926 is developed specifically for these requests and is easier to complete. When submitting an expanded access IND for single patient using Form 3926 a check box is available to request a waiver of full board IRB review. The waiver may be granted by the IRB chairperson or another designated IRB member before treatment use begins. The USC IRB submission must include the:

- Investigator Brochure or other source of information to determine risks and potential benefits
- Draft Informed Consent document
- Form FDA 3926

**Accessing FDA Form 3926** - Open the page in Internet Explorer or save the document as a PDF to your desktop before opening it up.

Expanded access for intermediate-size patient populations and widespread use of a treatment IND require USC IRB submission with Form 1571 or Form 1572. Information describing expanded access categories can be found at the following FDA website: [https://www.fda.gov/newsevents/publichealthfocus/expandedaccesscompassionateuse/ucm429624.htm#Expanded\\_Access\\_Categories](https://www.fda.gov/newsevents/publichealthfocus/expandedaccesscompassionateuse/ucm429624.htm#Expanded_Access_Categories)

The IRB will determine whether the criteria for approval have been met based on the applicable regulations ([21 CFR 56](#), [21 CFR 312.305](#) and [312.310](#)).

When the patient is a child provisions of [21 CFR 50.52](#) must be met to assure that the anticipated benefit to risk is at least as favorable to the child as available alternative treatment.

If the patient is considered vulnerable to coercion or undue influence additional safeguards should be included in the treatment plan to protect the rights and welfare of the patient.

The following links provide addition information:

- [For Physicians: A Guide to Non-emergency Single Patient Expanded Access Submissions](#)
- [Expanded Access \(Compassionate Use\)](#)
- [An Overview of FDA's Expanded Access Process and the New Individual Patient Expanded Access Application](#)
- [Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers Guide for Industry](#)

### Right to Try Act (S. 204)

Effective May 29, 2018 the [Right to Try Act \(S.204\)](#) created a second pathway for certain patients to access investigational drugs outside a clinical trial. This new pathway will co-exist with FDA's existing expanded access program. Drug manufacturers and institutions with whom physicians are affiliated can decide to continue to provide expanded access under the existing FDA program. Nothing in the new law prohibits an entity from filing an IND for a single patient expanded access treatment use, or from seeking IRB approval to ensure that a patient's interests are appropriately respected and protected, regardless of whether access is provided under an IND.

It is unknown at this time exactly how this new law will be implemented. A summary of the provisions follows:

- The new law applies only to investigational drugs. It does not apply to medical devices.
- It applies to individual or single patient treatment uses.
- It applies to investigational drugs that:
  - Have completed a Phase 1 clinical trial (defined under 21 CFR 312.21).
  - Have not been approved or licensed by FDA.
  - Are being actively studied in a clinical trial or are included in an application for approval has been filed with FDA.

### Treatment IND

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND [21 CFR 312.34](#) and [312.35](#) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

- The drug is intended to treat a serious or immediately life-threatening disease
- There is no satisfactory alternative treatment available
- The drug is already under investigation, or trials have been completed
- The trial sponsor is actively pursuing marketing approval

Treatment IND studies require prospective IRB review and informed consent.

### Open Label Protocol or Open Protocol IND

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued to enable the subjects and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review of the protocol and informed consent.

### Parallel Track

The FDA's Parallel Track policy 57 FR 13250 permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

## 18.3 Investigational Medical Devices

### *Definitions Related to Investigational Medical Devices*

<b>Medical Device</b>	A medical device is any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices also include reagents and test kits for in vitro diagnosis of disease and other medical conditions such as pregnancy.
<b>Significant Risk Device</b>	A device that presents a potential for serious risk to the health, safety, or welfare of a subject, and 1) Is intended as an implant; 2) Is used in supporting or sustaining human life; 3) Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or 4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
<b>Non-Significant Risk Device</b>	A device that does not meet the definition of a significant risk study. (A nonsignificant device should not be confused with the concept of "minimal risk" used in IRB regulations under 45 CFR 46.)
<b>510(k) Device</b>	A new device determined by the FDA to be substantially equivalent to an approved device. 510(k) devices are “cleared” by the FDA and may be marketed immediately.
<b>Investigational Device Exemption (IDE)</b>	An approved IDE permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device.

Medical devices range from simple products such as bandages and tongue depressors to complex products such as cardiac pacemakers, surgical lasers, orthopedic implants, and imaging systems and software. Medical devices also include diagnostic products such as pregnancy test kits. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects. The FDA has guidelines specific to informed consent for in vitro diagnostic (IVD) research studies using leftover human specimens that are not individually identifiable. FDA guidance link:

<http://www.fda.gov/downloads/medicaldevices/deviceregulationand%20guidancedocume>

[nts/ucm071265.pdf](#)

The FDA has several regulatory mechanisms for studying and approving new devices and modifications to existing devices. These regulatory mechanisms are based on the level of risk to participants. Investigators who are studying devices must provide the IRB with complete and accurate information about the regulatory status and risk level of each device.

An Investigational Device Exemption (IDE) permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device. Investigational use also includes clinical evaluation of new intended uses of legally marketed devices. The IDE regulations found at [21 CFR 812](#) describe three types of device studies:

### **Significant Risk Device Studies**

A significant risk device is an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
- Is for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject, or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

Significant risk device studies must follow all the IDE regulations. An IDE application must be approved by the FDA and the IRB before the study can begin.

### **Nonsignificant Risk Device Studies**

A nonsignificant risk device is one that does not meet the definition of a significant risk device. Studies of nonsignificant risk devices must follow the abbreviated IDE requirements at [21 CFR 812.2\(b\)](#). An IDE application is not required.



### IDE Exempt Studies

Certain device studies are exempt from IDE requirements, including studies using:

- A legally marketed device when used in accordance with its labeling (including 510(k) devices)
- A diagnostic device if it complies with the labeling requirements in [§809.10\(c\)](#) and, if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk; does not by design or intention introduce energy into a subject; and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure
- A device used for consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk
- The device is a custom device as defined in 21 CFR 812.3(b) unless the device is being used to determine safety or effectiveness for commercial distribution

### Determination of Risk Level

The study sponsor is responsible for the initial determination that a device poses significant or nonsignificant risk to subjects. If there is no industry sponsor, the Principal Investigator is considered to be the sponsor and must make the initial risk determination. The IRB must review the initial determination for each device study and make an independent risk determination. The FDA guidance document [Significant Risk and Nonsignificant Risk Medical Device Studies](#) is available to help distinguish significant from nonsignificant risk studies. This guidance document provides many examples of significant and nonsignificant risk devices. Sponsors, investigators, and IRBs may need to request additional assistance from the FDA to make the risk determination.

### Significant Risk Devices

The sponsor makes the initial determination that a device presents significant risk to subjects. If the sponsor determines it to be a significant risk device, the sponsor must submit an IDE application to the FDA. The study cannot begin until the FDA approves the IDE application. When the FDA receives an IDE application, FDA notifies the

sponsor in writing that the application was received and that an IDE number was assigned. The IDE application is considered approved 30 days after it was received by FDA, unless the FDA informs the sponsor within 30 days that the IDE application was not approved or that it must be modified.

The IRB must make an independent determination of device risk when reviewing the study. Because significant risk devices present more than minimal risk to subjects, all significant risk device studies will be reviewed by the full committee. In deciding if a study poses a significant risk, the committee will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. For example, if subjects must undergo a surgical procedure as part of the study, the IRB will consider the potential risks of the surgery in addition to the potential risks of the device.

The investigator cannot begin a significant risk device study until the IDE is approved and the USC IRB approves the study. The sponsor and investigators must comply with IDE regulations in conducting the study.

### **Nonsignificant Risk Devices**

The sponsor makes the initial determination that the device presents nonsignificant risks to subjects. The proposed study can then be submitted directly to the IRB for review, without an IDE application and without FDA notification or approval. The IRB reviews the study and makes an independent determination about the risk level.

The IRB determination is based on information provided by the sponsor. In deciding if a device presents nonsignificant risks, the committee will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. The sponsor must provide a statement that the study involves nonsignificant risk to subjects and an explanation why the study does not involve significant risks to subjects. The IRB may require additional information from the sponsor or investigator, including: a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures, any other information the IRB finds necessary to make a risk determination, whether other IRBs have reviewed the study and the determinations that were made, and the FDA's assessment of the device's risk (if the FDA has made such an assessment).

If the IRB agrees with the nonsignificant risk determination, the study can begin after the investigator receives IRB approval. The FDA does not have to be notified of IRB approval of a nonsignificant risk device study.

If the IRB does not agree with the sponsor's nonsignificant risk determination and instead finds that the study involves significant risk, the IRB will notify the investigator, and where appropriate, notify the sponsor. The sponsor must notify the FDA in writing (21 CFR 812.150(b)(9)) of the IRB determination. The IRB can review the study as a significant risk device study, but the study may not begin until FDA approves an IDE application or makes its own nonsignificant risk determination.

### Abbreviated IDE Requirements

Nonsignificant risk device studies must follow the abbreviated IDE requirements under [21 CFR 812.2\(b\)](#). These requirements address labeling of the device, IRB approval, informed consent, monitoring, and records and reports.

### IRB Responsibilities

The IRB must review the initial risk determination for each device study and make an independent determination of the risk. The determination is based on information provided in the device section of the iStar application. If the device information is incomplete or inaccurate, the IRB will not approve the study until the investigator provides additional information.

Investigators must describe the regulatory status of each study device in the iStar application as well as rationale for determining whether or not an IDE is required for the study. If the study requires an IDE, the IRB staff will verify that the IDE number provided in the iStar application matches the number provided in the sponsor's protocol or in FDA correspondence. The committee will discuss the study risks and make a determination about the device. This determination will be recorded in the meeting minutes. If an IDE number is not provided, the study will not be approved. The investigator will be asked to re-submit the application after obtaining the IDE number.

If the study is proposed as a nonsignificant risk device study, the committee will discuss the study risks and make a determination about the device. This determination will be recorded in the meeting minutes. The minutes will instruct the investigator to comply with the abbreviated IDE requirements.

If the study is proposed to be exempt from IDE requirements, the committee or expedited reviewer will confirm the exemption type proposed by the investigator. The IRB determination will be recorded in the meeting minutes or expedited review correspondence. For studies involving 510(k) devices, the IRB staff will check the FDA database to verify the regulatory status of the device. The IRB may require that the investigator obtain written documentation of 510(k) clearance and attach this documentation in the iStar application. A device with 510(k) clearance is a legally marketed device when used in accordance with its labeling.

### Off-Label Use of Devices (Treatment)

An IDE is not required when a health care provider uses an approved device to treat an individual patient for an unlabeled indication. This is referred to as “off-label” use, meaning the treatment is being used in a manner not specified in the FDA’s approved packaging label or insert. An IDE is not required because this use falls within the scope of medical practice and it is not research.

## 18.4 Sponsor-Investigators

USC investigators who initiate and submit IND or IDE applications to the FDA assume the responsibilities of both the investigator and the sponsor. Sponsor-Investigators must provide FDA documentation of their IND or IDE in the iStar application.

Sponsor-Investigators are required to complete and sign the [USC Sponsor-Investigator Agreement Form](#) and attach it in the iStar application. This agreement serves as an assurance that the investigator will review, be cognizant of, and comply with regulatory requirements of sponsor-investigators. The IRB may require the PI to receive training / education from the IRB Chair, an experienced IRB member, or other designee before beginning the research. FDA requirements and application links for an IDE and IND are listed below.

### IDE

A sponsor-investigator for an IDE protocol needs to submit an [FDA IDE Application](#) and must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities. This includes:

- The record keeping requirements of 21 CFR 812.140(b)
- The reporting requirements of 21 CFR 812.150(b) including annual IDE progress report to the IRB (and annual progress report to FDA if the IDE is for a significant risk device)
- The required notification under 21 CFR 812.150(b)(1) to the FDA and all participating investigators of any evaluation of an unanticipated adverse device effect within 10 working days of first receiving notice of the effect. Unanticipated adverse device effects are described in [Section 7.15 Reportable Events](#).

### IND

A sponsor-investigator for an IND protocol needs to submit an [FDA Form 1571](#) and must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:

- The recordkeeping and record retention requirements of 21 CFR 312.57
- The annual report requirements of 21 CFR 312.33 and safety reporting of 312.32 and
- Prompt reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic

The IND or IDE product must be stored, secured, dispensed, and documented in accordance with policies of the Institution where the test article will be used, such as Keck Hospital of USC, USC Norris Comprehensive Cancer Center and Hospital, Keck Medicine clinics, LAC+USC Medical Center, and other USC locations.

If the sponsor-investigator holding the IND or IDE leaves USC or transfers to USC, the sponsor-investigator is responsible for notifying FDA about the change in Institution and address.

For additional information, refer to:

[Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators.](#)

[OPRS – Drugs and Devices](#)

[Appendix G – USC Human Subjects Research Booklets](#)

### 18.5 Expanded Access (Compassionate Use) of Medical Device

The FDA [Expanded Access \(Compassionate Use\)](#) provision allows patients who do not meet eligibility criteria for a clinical trial to have access to an investigational device. This provision applies to an individual patient or a small number of patients for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. Patients must have a serious disease or condition and have no acceptable alternatives for treatment.

Both FDA approval and IRB approval are needed before expanded access use occurs. Submission for Compassionate Use is located in the Emergency Use application (iStar Item 1.6) The Compassionate Use provision differs from the [Emergency Use of Test Article](#) or [Humanitarian Use Devices](#) (HUD). Prior to treatment the sponsor must submit an IDE supplement and request approval for a compassionate use under section §812.35(a) in order to treat the patient(s). The IDE supplement should include:

- A description of the patient's condition and the circumstances requiring treatment
- A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
- An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
- The patient protection measures that will be followed (including informed consent, concurrence of IRB Chair, clearance from the Institution, independent assessment from uninvolved physician, and authorization from IDE sponsor)

- The number of patients to be treated (when use is of Small Group)

### **Physicians Responsibilities**

The physician should not treat the patient until FDA and the manufacturer approves the specific compassionate use of the device and the USC IRB Chair has approved the iStar application.

#### **Reporting and Monitoring Requirements**

The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.

Following the compassionate use of the device:

- A follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented
- Any problems which occurred as a result of device use should be discussed in the supplement and reported to the IRB as soon as possible.
- Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

### **IRB Responsibilities**

The IRB will acknowledge and evaluate the submission to determine whether the compassionate use met the eligibility criteria and complied with the regulatory requirements. Compassionate use is a clinical care activity, not research. Data obtained from compassionate use cannot be used for research purposes.

### **Compassionate Use for Multiple Patients**

Compassionate use is typically approved by the FDA for individual patients but may be approved to treat a small group. Clinician may treat multiple patients rather than an individual patient suffering from a serious disease or condition for which no adequate alternative therapy meets the medical need. In this case, the clinician should request access to the investigational device through the IDE sponsor. The sponsor should submit

to the FDA an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted to the FDA in an IDE supplement after all compassionate use patients have been treated.

More information can be found on the FDA website:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#compassionateuse>

### 18.6 Humanitarian Use Devices (HUD)

#### *Definitions Related to Humanitarian Use Devices (21 CFR 814)*

<b>Humanitarian Use Device (HUD)</b>	A device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year.
<b>Humanitarian Device Exemption (HDE)</b>	An authorization from the FDA to market an HUD; indicates the device does not pose unreasonable risk of injury to patient. The probable benefit outweighs risk of injury from use. Exempt from “effectiveness” requirements.

A special type of medical device, the Humanitarian Use Device (HUD), is intended to benefit patients with rare conditions or diseases (affecting fewer than 4,000 people in the United States per year) and that is exempt from the effectiveness requirements. The Office of Orphan Products Development determines if a device can be designated as an HUD. The FDA must approve a Humanitarian Device Exemption (HDE) application before the device can be marketed. The HDE authorization clears the HUD for marketing.

The use of the device does NOT constitute research; however, federal regulations require the local IRB approve the use of an HUD before it is administered to local patients. USC



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clinicians who wish to use an HUD must submit an iStar application and select “Use of Humanitarian Use Device (Not Research)” as the submission type. Initial IRB review is conducted at a Full Board meeting, but annual continuing review is conducted by an expedited reviewer.

The clinician submitting the IRB application must provide documentation to the IRB that the device’s sponsor has obtained an HDE. The device’s sponsor must document the following information in writing:

- The generic and trade name of the device
- The FDA HDE number (a six-digit number preceded by the letter H)
- The date of the HUD designation
- Indications for use of the device
- A description of the device
- Contraindications, warnings, and precautions for use of the device
- Adverse effects of the device on health
- Alternative practices and procedures
- Marketing history
- Summary of studies using the device

FDA regulations do not require an informed consent form for clinical use of an HUD (i.e., 21 CFR 50: see reference 7.5). However, sponsors often provide a sample consent form and the IRB or the Institution may require the investigator to use the template informed consent form specific for HUDs with all references to research eliminated.

The USC clinician must verify in the iStar application that the HUD is not being tested as part of a research study. The IRB is not required to determine whether the device is “significant risk” or “non-significant risk”. Investigators who intend to study the efficacy and safety of an HUD in research require an IDE. Clinicians will also be asked about intended off-label use of the HUD.

## 18.7 Emergency Use of a Test Article (Investigational Drug, Biologic or Device)

Emergency use is defined as the use of a test article in a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval ([21 CFR 56.102\(d\)](#)). The emergency use provision in the FDA regulations [21 CFR 56.104\(c\)](#) provides an exemption from prior review and approval by the IRB. The exemption allows for one emergency use of a test article without prospective IRB review for a subject in a life-threatening or severely debilitating situation in which no standard treatment is available.

- Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

FDA regulations require that any subsequent use of the test article at the Institution must have prospective IRB review and approval. Subsequent use includes a second use in the first subject or the use in another subject. An IRB application must be submitted immediately after the first emergency use if additional uses of the test article are anticipated. However, the FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the proposed use.

When there is time for prospective IRB approval before the test article is used, the investigator must complete an IRB application. The proposal will be scheduled for review at the next convened meeting. FDA regulations do not provide for expedited IRB approval by an expedited reviewer. Treatment cannot be initiated until IRB approval is obtained.

### Procedures for IRB Notification of Emergency Use

The treating physician must notify the IRB of any intended emergency use of a test article before the use occurs. This is done through the “New Emergency Use Application” activity in iStar. The physician must provide assurances that the proposed use of the test article meets the emergency use criteria and that an IND, IDE, or HDE will be obtained. The physician must submit the first part of the application to the IRB as notification of the intended use. If the physician proceeds with emergency use of the test article, the physician is required to notify the IRB within 5 working days of the use. This is done by completing and submitting the second part of the Emergency Use Application to the IRB. The IRB will acknowledge the emergency use at the next convened meeting. In the acknowledgment letter, the physician is reminded that subsequent uses of the test article require prior IRB approval.

Some manufacturers will not ship the test article to the physician without written agreement from the IRB. The physician will receive an acknowledgement notice from the IRB when the emergency use application is submitted. If this acknowledgement notice is not sufficient documentation for the sponsor to ship the test article, the physician should contact the IRB immediately for additional documentation.

### Emergency Use of an Investigational Drug or Biologic

The emergency use of an unapproved investigational drug or biologic requires an IND. The treating physician must contact the manufacturer to find out if the manufacturer will ship the drug or biologic for emergency use under the manufacturer’s IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means. Refer to [“Individual Expanded Access Involving Investigational New Drug”](#).

### Informed Consent

The treating physician is required to obtain informed consent of the subject or the subject’s legally authorized representative for emergency use of a drug or biologic, unless

both the treating physician and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject
- Time is not sufficient to obtain consent from the subject's legal representative
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

If the treating physician believes that immediate use of the test article is required to preserve the subject's life and if time is not sufficient to obtain an independent physician's assessment, the treating physician should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

### **Emergency Use of an Investigational Device**

Unapproved devices are normally used only in approved clinical studies conducted under an IDE. Emergency situations may arise in which there is a need to use an investigational device in a manner inconsistent with the clinical study or by a treating physician who is not part of the clinical study.

Emergency use of an unapproved device may occur before an IDE is approved if all the following criteria are met:

- The subject has a life-threatening disease or serious condition requiring immediate use
- There are no generally accepted alternative treatments
- There is no time to obtain FDA approval of an IDE

If an IDE exists, authorization from the IDE sponsor should be obtained. The sponsor is responsible for reporting the emergency use to the FDA within 5 working days. If no IDE exists, the treating physician is responsible for reporting the emergency use to the FDA.

The treating physician has the following responsibilities:

- Obtain an independent assessment by a physician who is not participating in the investigation
- Obtain institutional clearance according to institutional policy (if required by the healthcare facility)
- Obtain concurrence from the IRB Chair
- Obtain authorization from the sponsor if an IDE exists
- Obtain informed consent for the emergency use

### **Informed Consent**

The treating physician is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the treating physician and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following ([21 CFR 50.23](#)):

- The subject is confronted by a life-threatening situation necessitating the use of the device
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject
- Time is not sufficient to obtain consent from the subject's legal representative
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

### Independent Physician Assessment

If the treating physician believes immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's assessment, the treating physician should make the determination. Within 5 working days after the use of the article, the treating physician must have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article ([21 CFR 50.23](#)).

### 18.8 Planned Emergency Research with Exception from Informed Consent

Planned emergency research is a rare type of research that allows participants to be enrolled without prior informed consent. It differs from emergency use of a test article described above. Investigators who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB. All of the following conditions must be present for emergency research with an exception from informed consent requirements, as described in 21 CFR 50.24:

- The human subjects are in a life-threatening situation that necessitates urgent intervention
- Available treatments are unproven or unsatisfactory
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention
- Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition
- The intervention must be administered before consent can be obtained from the subject's legally authorized representative
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation
- Participation in the research holds out the prospect of direct benefit to the subjects

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- The clinical investigation could not practicably be carried out without the waiver

Planned emergency research refers to research planned to occur in emergency settings, and it requires prospective IRB approval. Studies meeting the criteria for an exception from informed consent for emergency research must be approved by the FDA and have a separate IND or IDE.

Before the research is approved, investigators must consult with representatives of the communities where the research will be conducted and from which participants will be drawn and publicly disclose the research plan and potential risks and benefits to the communities. Investigators must also publicly disclose the results of the trial to the community after the trial is completed. An independent data monitoring committee must be established to exercise oversight of the research.

The IRB must ensure that there are appropriate procedures in place to inform subjects, their legally authorized representative, or their family members of their inclusion in the study, details about the study, the subject's right to discontinue participation, and other information contained in the informed consent form. This must be done at the earliest feasible opportunity.

The IRB evaluates the responses provided in all corresponding subject sections of the iStar submission application to determine that the study will be conducted in accordance with applicable regulations and requirements.

The IRB and/or the investigator will only provide advance notice of these protocols to the Office for Human Research Protections (OHRP) when the research is not subject to FDA regulations. Information about OHRP's Informed Consent Requirements in Emergency Research can be found at <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-research-informed-consent-requirements/index.html>

Additional responsibilities of investigators, the IRBs, and the sponsors are described in the FDA's [Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors – Exception from Informed Consent Requirements for Emergency Research](#).

### **Research Supported by the Department of Defense (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The USC IRBs do not approve exceptions from consent

in emergency medicine research funded by DOD unless a waiver is approved by the Secretary of Defense.

### 18.9 Dietary Supplements

Dietary supplements are regulated by the FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Dietary supplements include vitamins, minerals, herbs, botanicals, amino acids, and other dietary substances intended to supplement the diet.

Investigators who wish to use dietary supplements in clinical studies will be asked to add information about each dietary supplement product to the iStar application. This should include the composition of the product and whenever possible, information about previous human use, testing, and safety.

Although dietary supplements are not subject to the same FDA regulations as drugs, clinical testing of a dietary supplement may still require an Investigational New Drug (IND) application. If the intent of the study is to evaluate a dietary supplement's effects on the normal structure or function of the body, no IND is required. If the intent of the study is to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required before the IRB will approve the study. Investigators should review the FDA guidance document "[Investigational New Drug Applications \(INDs\) – Determining Whether Human Research Studies Can Be Conducted Without an IND](#)" when planning a clinical study using a dietary supplement. The IRB may ask investigators to contact the FDA for a written opinion about the need for an IND for clinical studies of dietary supplements. Additional information is available in the FDA guidance document "[Botanical Drug Products](#)."

### 18.10 Screening Procedures and Consent for FDA Research

The following is excerpted from the FDA Information Sheet "Screening Tests Prior to Study Enrollment": <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm>

In general, for some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of



entry into a study with a prospective subject without first obtaining consent, **informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.**

Screening may qualify as a minimal risk procedure [21 CFR 56.102(i)] and the IRB may choose to use expedited review procedures [21 CFR 56.110] to approve such screening. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate.

Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a screening consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would be followed.

### **HIPAA Waiver for Screening Medical Records**

HIPAA regulations apply to the screening process if it involves review of medical records. Investigators must obtain prospective HIPAA authorization from participants or apply for a partial waiver of HIPAA authorization for recruitment and screening. Refer to [Section 11.5 – Health Insurance Portability and Accountability Act \(HIPAA\)](#) for additional information.

### **18.11 Data Retention Requirements Related to Subject Withdrawal from FDA-Regulated Research**

In FDA-regulated research, specific data retention requirements and disclosure to subjects apply, as described below:

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be

removed. The consent document cannot give the participant the option of having data removed.

- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.
- The researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

### 18.12 Registration of Clinical Trials and Other Types of Research

USC researchers are expected to comply FDA, NIH, and ICJME requirements to register clinical trials in [clinicaltrials.gov](https://clinicaltrials.gov). FDA regulations require that all “applicable clinical trials” be registered in the [ClinicalTrials.gov](https://clinicaltrials.gov) clinical trials data bank (FDAAA 801). NIH requires that all clinical trials meeting the [NIH definition](#) of “clinical trial” must be registered to [clinicaltrials.gov](https://clinicaltrials.gov). Studies that are intended to be published in an ICMJE must also be registered in [clinicaltrials.gov](https://clinicaltrials.gov) prior to subject enrollment.

ClinicalTrials.gov is a public registry and results database of clinical trials supported by public or private funds.

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The “Responsible Party” (the sponsor or the principal investigator designated by the sponsor) must register and report results of applicable clinical trials involving:

- Drugs and Biologics: controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation or
- Devices: controlled trials with health outcomes, other than small feasibility studies, and pediatric post market surveillance

*"Applicable clinical trials"* generally include interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- Have one or more sites in the U.S
- Involve a drug, biologic, or device that is manufactured in the US (or its territories) and is exported for research
- Be conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

For more information on definitions of terms, refer to [FDAAA 801 Requirements](#). It is important to note that FDA and HHS regulations are inconsistent in the use of the terms “clinical trials” and “clinical investigation”. For more information, refer to 21 CFR [50](#), [56](#), [312](#) and [812](#).

Registration and results reporting are required for applicable clinical trials; however, ClinicalTrials.gov allows voluntary reporting of other studies that:

- Are in conformance with any applicable human subject or ethics review regulations (or equivalent) and
- Are in conformance with any applicable regulations of the national (or regional) health authority (or equivalent)

Investigators may choose to register a study that is not an applicable clinical trial as a condition to publish study results in a journal.

FDA regulations require reporting of results from registered trials. The Responsible Party must generally report results no later than 12 months after the trial completion date. Results must include participant baseline characteristics, participant flow diagram,

outcomes, and adverse events. Instructions for submitting results are available at [ClinicalTrials.gov](http://ClinicalTrials.gov). FDA also requires sponsors or investigators to certify compliance with ClinicalTrials.gov registration when submitting certain applications to the FDA. Form FDA 3674 is used to certify compliance.

### Mandatory Informed Consent Language

FDA regulations require that informed consent forms contain specific language about clinical trial registration. Informed consent documents for applicable clinical trials or any study that will be registered in ClinicalTrials.gov must contain the following language in the Confidentiality section:

“A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.”

### Federal Enforcement

Investigators who fail to comply with registration or reporting of results on ClinicalTrials.gov can be penalized. Penalties include civil monetary fines and withholding of grant funds if the study is federally funded.

### Other Registration Requirements

#### National Institutes of Health

NIH requires all grantees, regardless of whether or not they are the Responsible Party, to certify that they are complying with FDAAA 801 in grant applications and progress reports. Grantees must certify that the responsible party has made all required submissions to ClinicalTrials.gov for applicable clinical trials funded in whole or in part by the NIH. Click here for more details about [Certifying Compliance with FDAAA in NIH Applications and Progress Reports](#). NIH certification is different from the FDA certification described above.

### Centers for Medicare & Medicaid Services (CMS)

CMS now requires providers and suppliers to report an 8-digit clinical trial number (NCT number) assigned by ClinicalTrials.gov on claims for items/services furnished pursuant to clinical trials that qualify for coverage as set forth in the Medicare National Coverage Determination Manual. This requirement became effective 1/1/2014. Any qualifying clinical trial that bills tests and procedures to Medicare must be registered to receive payments from CMS. Claims submitted without the NCT number will be returned to providers for reprocessing and addition of the NCT trial number.

### Journals

Journals may require registration of clinical trials and other types of health-related interventions in order to publish manuscripts. The International Committee of Medical Journal Editors (ICMJE) policy requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry prior to enrollment of the first subject. Investigators should carefully review registration requirements at [ICMJE Clinical Trials Registration](#).

### How to Register a USC Study

#### **For industry-sponsored research:**

The industry sponsor is responsible for registration of the research on ClinicalTrials.gov. USC Clinical Trials Office (CTO) will verify that the sponsor has registered the trial and provided the NCT number.

#### **For investigator-initiated research:**

Investigators in the Cancer Center should contact the Clinical Investigations Support Office ([CISO](#)) for assistance in registering their research on ClinicalTrials.gov.

Investigators who are not in the Cancer Center should contact the Associate Director of the Department of Contracts and Grants to request a user account for ClinicalTrials.gov:

Email: [jeanbcha@usc.edu](mailto:jeanbcha@usc.edu)

Telephone: 323-442-2825

Webpage: <https://research.usc.edu/clinical-trials-at-usc/9309-2/>

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For more information on registration of research go to: [ClinicalTrials.gov](https://clinicaltrials.gov),

### *Helpful Links*

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- FDA “Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions”  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126838.pdf>
- Clinicaltrials.Gov Protocol Registration System  
<http://prsinfo.clinicaltrials.gov/index.html>
- USC Vice President of Research Memorandum “ICMJE Journals Require Advanced Registration of Human Studies”  
[https://oprs.usc.edu/files/2014/04/Registration-of-Human-Studies\\_4-7-14.pdf](https://oprs.usc.edu/files/2014/04/Registration-of-Human-Studies_4-7-14.pdf)
- ICMJE List of Journals Following the ICMJE Recommendations  
<http://www.icmje.org/journals-following-the-icmje-recommendations/>

	Chapter 19: <b>Continuous Quality Improvement (CQI)</b>
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## **Chapter 19**

# **Continuous Quality Improvement (CQI)**

This chapter describes the USC Continuous Quality Improvement Program objectives, activities, and components. A detailed list of quality improvement activities outlines major components of the Program. The chapter concludes with an overview of investigator and IRB assessments and audits.

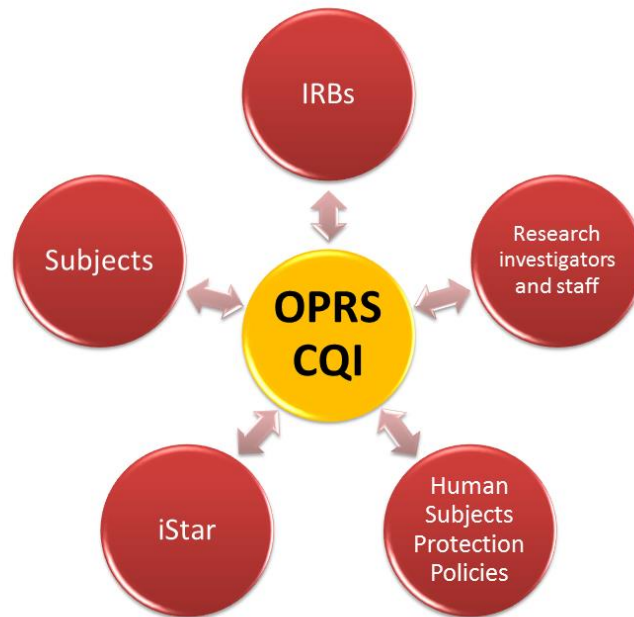
## **19.1 The Continuous Quality Improvement (CQI) Program**

The Human Subjects Protection Program (HSPP) conducts Continuous Quality Improvement (CQI) activities to measure and improve HSPP effectiveness, quality, and compliance with IRB policies and procedures, and applicable federal, state, local laws, and national accreditation standards. Outcomes of CQI activities are fed back into the process, resulting in improved protections for human subjects and increased efficiency. The CQI Program:

- develops and maintains USC Human Research Protection Program (HSPP) according to national best practices, regulations and guidelines
- keeps investigators cognizant of rules, corrects procedural errors, and
- increase protections for human research participants
- auditing and assessing investigator compliance with the HSPP policies and procedures and IRB requirements



## Continuous Quality Improvement (CQI) Program Diagram



### 19.2 USC CQI Activities

In addition to developing and maintaining policies, the HSPP creates resources to facilitate compliance in the USC research community. Below is a list of initiatives that make up and support CQI activities:

#### **Human Subjects Teleconferences**

Each month OPRS hosts a teleconference for IRB Directors and Chairs to share ideas and discuss human subjects protections developments and their impact on the Program.

#### **HSPP Executive Committee**

Monthly meetings are held amongst OPRS Executive Director and IRB Chairs and Directors from both campuses to discuss updates to regulations, implementation of new procedures, and best research practices.

#### **Education Sessions**

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OPRS and the IRB offer educational sessions on introduction to human subjects training, use of the electronic IRB application system and informed consent documentation to the USC research community.

### **Classroom Education Sessions**

OPRS, the IRB, and IRB Student Mentors offer classroom education as guest lecturers to discuss human subjects protections with students (incoming PhD students, medical students, undergrad scholars).

### **Booklets**

OPRS creates many booklets (available in hard copy and online) to educate student and researchers on a range of topics including students and research, conducting research using human subjects, mentoring USC student researchers, informed consent in human subjects research.

### **OPRS and IRB Website**

The website provides the latest information to the USC research community including guidance, consent templates, policies, educational resources, and contact information. Website analytics are reviewed periodically to determine web traffic, reader interest and improve site content.

### **Listserv Newsletter**

OPRS distributes a periodic newsletter to keep the USC research community informed of updates in regulations, policies, best practices, and relevant research news.

### **Research Coordinator Outreach and Bulletin**

Information specific for coordinators and research support staff is communicated through a coordinator bulletin and quarterly meetings. Featured topics include educational sessions, coordinator events and networking opportunities, coordinator FAQs, national coordinator resources and articles of interest.

### **IRB Student Mentor**

The OPRS graduate assistant serves as IRB liaisons by meeting with student researchers and providing one-on-one assistance and training. The student mentor is a full voting IRB member and represents USC students in IRB deliberations. Student mentors bring student concerns to policy meetings and also review OPRS documents for student perspective.

### **Annual IRB Survey**

Each year, users of the IRB application system are invited to complete an online anonymous survey to provide feedback about the IRB system and offer suggestions on how to improve the review process. The surveys show trends over time and identify problems and issues. A summary of the survey results is publicly disseminated to the research community on the listserv and HSPP website; detailed results are provided to the Institutional Official and the IRBs. Feedback often results in educational opportunities, policy changes and iStar system process changes.

### **iStar Development Meetings**

Representatives from OPRS, USC IRBs and Children's Los Angeles IRB meet with iStar personnel twice per month to address iStar upgrades, problems, glitches and solutions. Also, iStar issues and suggestions identified at various stages of the CQI process are addressed and discussed at these meetings.

### **Policies and Procedures Review and Updates**

HSPP Policies and Procedures are regulatory updated by the Human Subjects Working Group (OPRS, USC IRBs). Changes to Policies and Procedures are communicated to the IRB members, IRB staff, investigators, and research staff via the Human Subjects Newsletter. The Policies are available on the HSPP website.

### **IRB Member and Administration Education**

OPRS arranges monthly educational sessions for IRB members as well as periodic IRB administration educational lunches to discuss best practices, upcoming policy changes and other topics.

### **Community Outreach**

OPRS hosts annual meetings and teleconferences with communities to discuss emerging issues and share information. Additionally, OPRS created and regularly updates the "What It Takes to be an IRB Community Member" handbook (<https://oprs.usc.edu/files/2013/05/Community-Member-Booklet-5.1.13.pdf>). The handbook is nationally praised and has been adapted by various Institutions to supplement community member training.

### **Collaboration and Networking with Other Institutions**

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The HSPP collaborates and networks with other Institutions regularly to discuss best practices in policy and guidance development. Additionally, collaborative efforts with local partner Institutions reduce duplicative review of studies conducted at USC and either partner Institution (Children's Hospital Los Angeles and Cedars-Sinai Medical Center).

### **Flexibility Coalition**

The Coalition was originally established to discuss reducing the administrative burden on non-federally funded, no more than minimal risk projects. Teleconferences and in-person meetings are regularly scheduled to share, discuss and brainstorm ideas related to flexibility in the IRB review process. The Coalition is now more than 170 members strong.

### **California Coalition**

This Coalition is a network for institutions to collaborate with each other and share quarterly information on state and federal legislation affecting human subject research and educational topics of interest.

### **Audits**

Not-for-cause audits of research studies are conducted by OPRS; for-cause audits are conducted by the IRB. OPRS and IRB personnel also conduct assessments of IRB operations and the iStar system to identify trends and issues related to study approval times, IRB and investigator response time, IRB workload, and changes or deficiencies in policy implementation or process. Refer to the rest of this chapter for additional information.

For a list of more CQI activities at USC, visit: [Continuous Quality Improvement](#)

## **19.3 Audits and Assessments**

### **Audits For-Cause**

For-cause audits are reactive, direct, and aimed to investigate or substantiate an allegation or complaint received by the Human Subjects Protection Program (HSPP). Allegations or complaints may be submitted to the HSPP through written correspondence, anonymous phone call, or other avenues. Information received from a sponsor, the FDA, a

whistleblower, the IRB, IRB Chair, OPRS, an investigator, or a subject may all lead to a for-cause audit. Audits may also be initiated in response to protocol amendments, continuing reviews, and other submissions or communications with the IRB. Additionally, funding agencies may request a for-cause audit due to allegations of noncompliance, adverse events, or other causes of concern.

Low-risk/ non-clinical studies rarely warrant a for-cause audit. A main goal of for-cause audits is to collect sufficient information for the IRB to determine a course of action on serious or continuing non-compliance, or reported allegations and complaints. For-cause audits are conducted by IRB and OPRS personnel.

### Audit Procedures

The IRB Chair or Vice-Chair initiates for-cause audits based on an allegation, complaint, deficiencies found by IRB review activities, and/or information from media or scholarly reports.

The IRB discussion of the allegation and subsequent determination are documented in the IRB meeting minutes.

The following items/processes may be inspected:

- IRB (iStar) submissions and communications
- Researcher Files

If the investigator is a student researcher, the IRB may request to have the files inspected in the faculty advisor's office

- Research Case Report Forms (CRF)
- Informed Consent (IC) Documents
- Review of Consent Process

### Quality Assessments (Not For-Cause)

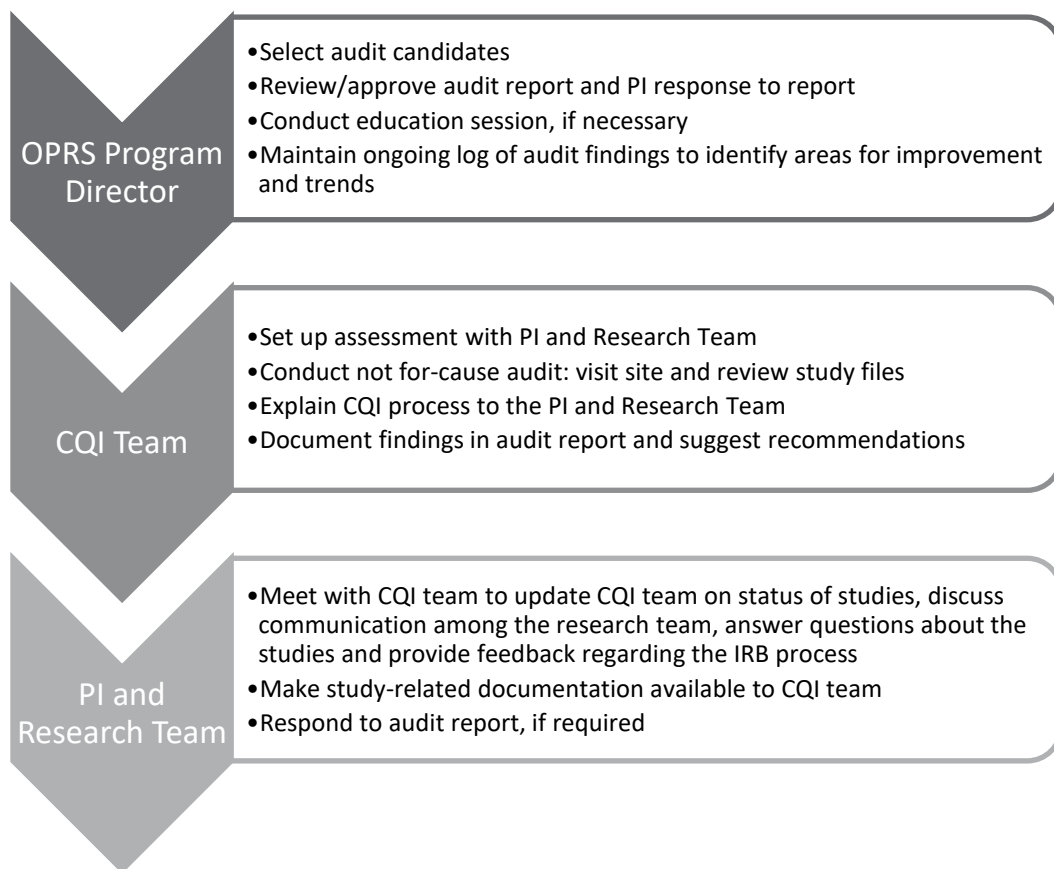
Quality assessments are not-for-cause assessments conducted by designees of the HSPP. The assessment team performs up to 10 assessments/re-assessments annually. In some cases, a follow-up assessment may be conducted to ensure compliance has been effected. Results of these assessments are educational and not routinely submitted to the IRB

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unless deemed necessary by OPRS. Research studies are chosen for quality assessment by OPRS/IRB staff using the following criteria:

- Schools and/or departments that submit high volumes of studies to the IRBs
- Investigators who have a high volume of active protocols
- Investigator-initiated protocols
- Studies including vulnerable subjects
- Studies conducted outside of the United States
- Recommendation by IRB staff

### Procedures for Investigator Visit Assessment



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OPRS notifies the Principal Investigator in writing of being selected for the CQI assessment. The CQI team schedules the assessment with the Principal Investigator (PI) and/or research team. The CQI team may request updated subject enrollment numbers for each IRB approved study to guide the assessment.

During the site visit, the CQI team conducts some of the following activities:

- Interviews the PI/research team to assess their knowledge of the study procedures
- Solicits feedback from researchers on the IRB process
- Inspects documentation that subjects met inclusion criteria
- Inspects study records and storage facilities
- Inspects documents and coding mechanisms used to protect confidentiality
- Reviews documentation of adverse events and unanticipated problems

After the assessment, the CQI team prepares a report summarizing findings or recommendations. Once reviewed and approved by the OPRS Program Director, the final report is forwarded to the PI. If findings are identified, the Principal Investigator must submit a response addressing each deficiency and include an action plan to prevent similar deficiencies in the future. In some cases, a follow-up assessment and/or training session(s) may be required.

If serious and/or continuing non-compliance is found, the CQI assessment report will be submitted to the IRB Chair and/or the IRB. The IRB will make recommendations to correct any issues of serious and/or continuing noncompliance. Refer to [Section 20.8 - Procedure for Handling Reports of Noncompliance](#) for more information.

The CQI team maintains a record of audit findings which is also used to identify trends and areas that are difficult or confusing for investigators. OPRS reviews audit findings to determine if improvements to the IRB process, electronic submission system or educational materials can be made to promote investigator compliance. When improvements to the system are identified, OPRS works with the IRB and/or iStar team to implement such changes.

### Audits by External Entities

External audits may be conducted by regulatory agencies (FDA, OHRP), a sponsor, or other entities external to USC (AAHRPP). External audits may be conducted for-cause or not for-cause.

#### For-cause

For-cause audits by entities external to USC may arise from an anonymous complaint, an unanticipated problem reported by the investigator to a sponsor or federal agency (FDA), noncompliance reports, or other. For-cause audits may arise from a self-report or be complaint-driven.

#### Not-for-cause

Routine, not for-cause audits may be conducted by entities external to USC. Investigators or sponsors may hire consultants to review a protocol, clinical practices, or other aspects of research. Clinical trial sponsors frequently send trial monitors to verify data integrity and adherence to regulatory requirements.

### 19.4 Assessments of IRB Processes

OPRS assesses internal IRB processes on an ongoing basis. These are primarily done through iStar-generated reports.

Assessment of the IRB process includes:

- Review of IRB minutes and Full Board meeting agendas, paying particular attention to subject complaints, adverse events, and ad hoc agenda items (miscellaneous problems/issues/suspensions/audits)
- Examination of IRB staff pre-reviews for accuracy.
- Review of official IRB letters for accuracy, correct regulatory citations, and clarity
- Review of researcher feedback/complaints



## **Chapter 19: Continuous Quality Improvement (CQI)**

- Review of the various forms and guidance documents found on the IRB websites, functionality of the website and hyperlinked documents
- Analysis of IRB processes (Not Human Subjects Research / Coded Data short application, other) to identify process issues
- Monitoring of new IRB staff members for accuracy, and the proper application of regulations and USC policies
- Review of ad hoc items as necessary

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# Chapter 20

## Reportable Events, Noncompliance, Suspensions, and Terminations

This chapter contains regulatory requirements\* for reportable events for both the investigator and the IRB. The following outline provides the contents of the chapter.

\*Written policies for ensuring prompt reporting to the IRB, appropriate Institutional Officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others are required by 45 CFR 46.103(b)(5), 21 CFR 56.108(b)(1) and 21CFR 812.3 and 812.150(a).

\*Definitions used in this policy come from [OHRP's Guidance on Unanticipated Problems and Adverse Events](#), dated January 15, 2007, ["FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection"](#) dated January 2009 and FDA's [Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans](#), dated September 29, 2010.

### Part One: Investigator Sections

- Adverse Events
- Unanticipated Problems Involving Risks to Subjects or Others
- Adverse Events that are Unanticipated Problems
- Adverse Device Effects

### Part Two: IRB and Institutional Sections

- IRB Procedure for Handling Reports of Adverse Events
- IRB Reporting of Adverse Events that are Unanticipated Problems
- IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others (UPX)
- Procedure for Handling Reports of Alleged Noncompliance

- Suspension or Termination of IRB Approval
- IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others

### PART I – INVESTIGATOR PERSPECTIVE

## 20.1 Adverse Events

The FDA defines adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” in the [Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans](#).

OHRP defines adverse events as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.” (See [Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)”)

Adverse events (AEs) encompass both physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. A small number of AEs are also *unanticipated problems involving risks to subjects or others (UPX)*.

### Internal and External Adverse Events in Multicenter Clinical Trials

In the context of multicenter clinical trials, AEs are characterized as either ***Internal AEs*** or ***External AEs***. When USC participates in a multicenter clinical trial, ***Internal AEs*** are those AEs experienced by subjects enrolled by the USC investigator(s), whereas ***External AEs*** are those AEs experienced by subjects enrolled by investigators at other Institutions engaged in the clinical trial. In the context of a single-center clinical trial conducted at USC, all AEs would be considered ***Internal AEs***. AE reporting requirements may vary depending upon agreements with multi-site collaborations, MOUs, and sIRB.

### Internal Adverse Events at USC

The USC investigator typically becomes aware of an Internal Adverse Event directly from the subject, another collaborating USC investigator, or the subject's healthcare provider. Upon becoming aware of an Internal AE, the investigator should evaluate whether the AE should be reported. If it is **unexpected; related or possibly related** to the study; and is either **serious** or suggests that the research places subjects or others at a **greater risk of harm** (physical or psychological) than was previously known or recognized, it should be reported to the IRB. The investigator must also ensure that the AE is reported to a monitoring entity (such as the research sponsor, a coordinating or statistical center, an independent research monitor, or a DSMB/DMC) *as required under the monitoring provisions described in the IRB-approved protocol*.

If the investigator determines that an AE is not reportable, but the monitoring entity subsequently determines that the AE does in fact represent a UPX (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

### Investigator Evaluation of Internal Adverse Events

Internal adverse events must be evaluated to determine whether they are:

#### Unexpected

Any adverse event occurring in one or more subjects participating in a research protocol for which the nature, severity, or frequency are **not** consistent with either:

- the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in:
  - the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
  - other relevant sources of information, such as product labeling and package inserts, or

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- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event

The vast majority of AEs occurring in the context of research are expected in light of:

- the known toxicities and side effects of the research procedures
- the expected natural progression of subjects' underlying diseases, disorders, and conditions, and
- subjects' predisposing risk factor profiles for the AEs. Thus, most individual AEs do not meet the first criterion and do not need to be reported because they are "expected"

### Related

Related or possibly related to participation in the research (in this document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research). Adverse events may be caused by one or more of the following:

- the procedures involved in the research including the drug, biological, device, or other intervention
- an underlying disease, disorder, or condition of the subject, or
- other circumstances unrelated to -the research or any underlying disease, disorder, or condition of the subject

In general, AEs that are determined to be at least partially caused by (a) would be considered related to participation in the research, whereas AEs determined to be solely caused by (b) or (c) would be considered unrelated to participation in the research.

### Serious

An event is defined as being serious if the event adversely alters the relationship between risks and benefits. Serious events include:

- Inpatient hospitalization or prolongation of hospitalization

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- Life-threatening reactions
- Persistent or significant disability/incapacity or permanent harm or disability (either physical or psychological)
- A congenital anomaly/birth defect in the offspring of the subject
- Jeopardizes the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- A breach of confidentiality that may have a negative consequence
- Results in death or places subject in immediate risk of death

The investigator's evaluation of the event is critical. Events that are unexpected, related to study participation, and serious must be submitted to the IRB for review. Events that do not meet these criteria do not have to be submitted to the IRB. If they are submitted, the event is auto-acknowledged and filed electronically.

### Investigator Reporting of Internal Adverse Events to the USC IRB

#### **Time-frame and mechanism of reporting:**

AEs that are unexpected, related or possibly related, and are either serious or place subjects or others at a greater risk of harm than was previously known or recognized, must be reported to the IRB through iStar, using the Reportable Event application. Reporting to the USC IRB must be as soon as possible, but not later than 10 working days after the investigator becomes aware of the event.

#### **For submission of an adverse event, include:**

- A detailed description of the adverse event, incident, experience, or outcome
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the event. Protocol changes and informed consent changes must be submitted through an iStar amendment application which may accompany (but more often follows) the submission of the event.

### External Adverse Events

**External AEs** are events experienced by subjects enrolled at non-USC Institutions. Very few External AEs need to be reported to the IRB. An External AE should be submitted only when it meets the criteria for reporting (the AE is unexpected, related to the research, and serious) AND it meets the following additional criteria: (a) it occurred at a non-USC site in the same trial that the USC investigator is conducting OR (b) it occurred with the same drug that is being used at USC, but under a different protocol and/or different trial, and the event resulted in a change to the risk/benefit ratio, protocol, and/or informed consent. External AEs are submitted to the IRB through iStar, using the Reportable Event application. These external adverse events are auto acknowledged and filed electronically. They are available for review at the time of continuing review. AE reporting requirements may vary depending upon agreements with multi-site collaborations, MOUs, and sIRB.

## 20.2 Unanticipated Problems Involving Risks to Subjects or Others

### Defining Unanticipated Problems Involving Risks to Subjects or Others (UPX)

The term **unanticipated problems involving risks to subjects or others (UPX)** is found (but not defined) in the HHS regulations at 45 CFR 46.103(b)(5), and is found in the Food and Drug Administration regulations at 21 CFR 56.108(b)(1).

An incident, experience, or outcome that meets the criteria for a UPX (below), generally is significant enough to warrant consideration of changes in the research protocol, informed consent process, informed consent document, or corrective actions to protect the safety, welfare, or rights of subjects or others.

A UPX includes any incident, experience, or outcome that meets **all** of the following criteria:

- **unexpected** (in terms of nature, severity, or frequency) given:
  - the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and

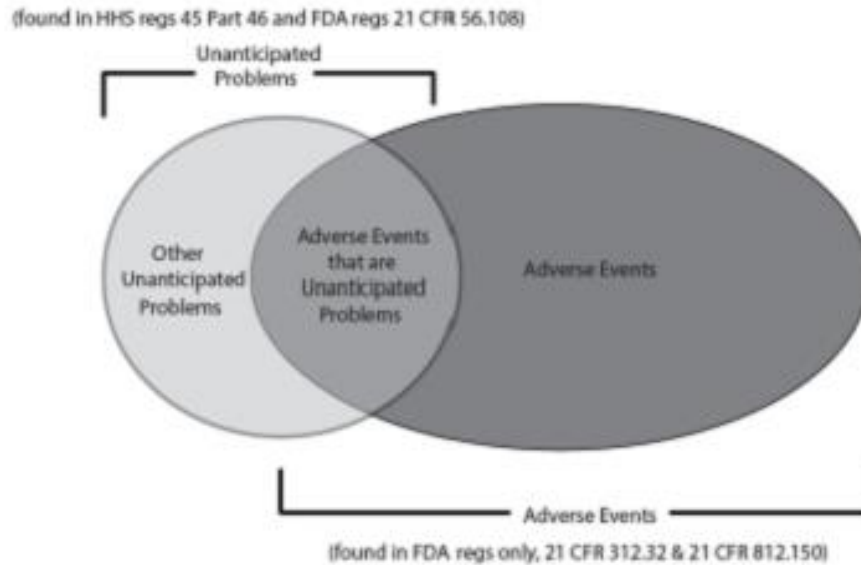


- the characteristics of the subject population being studied
- **related or possibly related to participation in the research** (in this document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research), and
- suggests that the **research places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) **than was previously known or recognized**

### Examples of Unanticipated Problems Involving Risks to Subjects or Others

- A breach in confidentiality that involves risk to that individual or others, such as a PI's laptop is stolen, and it contains identifiable medical information and research data about subjects (if laptop is encrypted, data is not considered "identifiable")
- Subject complaints that cannot be resolved by the research team or which indicate increased or unexpected risks
- Any accidental or unintentional change to the IRB-approved protocol that increases risk or decreases benefit, affects the subject's rights, safety, welfare, or affects the integrity of the resultant data
- Any publication in the literature, safety monitoring report including a Data and Safety Monitoring Board report, interim result, or other finding that indicates an unexpected change to the risk/benefit profile of the research

Adverse events are a larger and all-inclusive category of events in comparison to unanticipated problems. Only a small subset of adverse events will also meet the definitions/criteria "involving risks to subjects or others" (UPX) and require reporting to the FDA and OHRP, or equivalent office within the appropriate Federal department or agency. See the flow chart below to determine if an adverse event is a UPX and must be reported. For additional information, refer to [Section 9.8](#) and [Section 7.14](#).



### 20.3 Adverse Events that are Unanticipated Problems

When adverse events should be considered unanticipated problems (UPX) that merit reporting to the IRB is a critical question. In the years since the IRB and IND regulations were issued, changes in the conduct of clinical trials (for example, increased use of multi-center studies and international trials) have complicated the reporting pathways for adverse event information described in the regulations.

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events must be communicated among investigators, sponsors, and IRBs as follows:

- Investigators are required to report promptly “to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately” (§ 312.64(b)).
- Sponsors are specifically required to notify all participating investigators (and FDA) in a written report of:
  - any adverse experience associated with the use of the drug that is both serious and unexpected

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- any finding from tests in laboratory animals that suggests a significant risk for human subjects, and
  - new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use
- Investigators are required to report promptly “to the IRB... all unanticipated problems involving risks to human subjects or others,” including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

The practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative. Reports of individual External AEs often lack sufficient information to allow investigators or the IRB at each Institution engaged in a multicenter clinical trial to make meaningful judgments about whether AEs are unexpected, are related or possibly related to participation in the research, are serious or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

For multicenter research protocols, when a local investigator at one Institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an AE or UPX, the investigator should consult with the study sponsor or coordinating center regarding the proposed changes because changes at one site could have significant implications for the entire research study.

Accordingly, to satisfy the investigator’s obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor’s assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB, and because the investigator was copied on the report from the sponsor to the IRB, FDA would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

### Coordinating Center Reporting Responsibilities

A coordinating center in multicenter research is the Institution responsible for collecting all reports of adverse events and UPXs for all study sites. Coordinating centers should only report individual AEs to investigators and IRBs at all Institutions when a determination has been made that the events meet the criteria for a UPX. Ideally, AEs occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with the monitoring plan described in the IRB-approved protocol.

### Sponsor Determination of Adverse Events that Are Unanticipated Problems

In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators—to make a determination about whether an AE is an unanticipated problem. Furthermore, the regulations require the sponsor of an IND to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (§ 312.32).

For multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

#### **FDA Examples of Adverse Events that are Unanticipated Problems:**

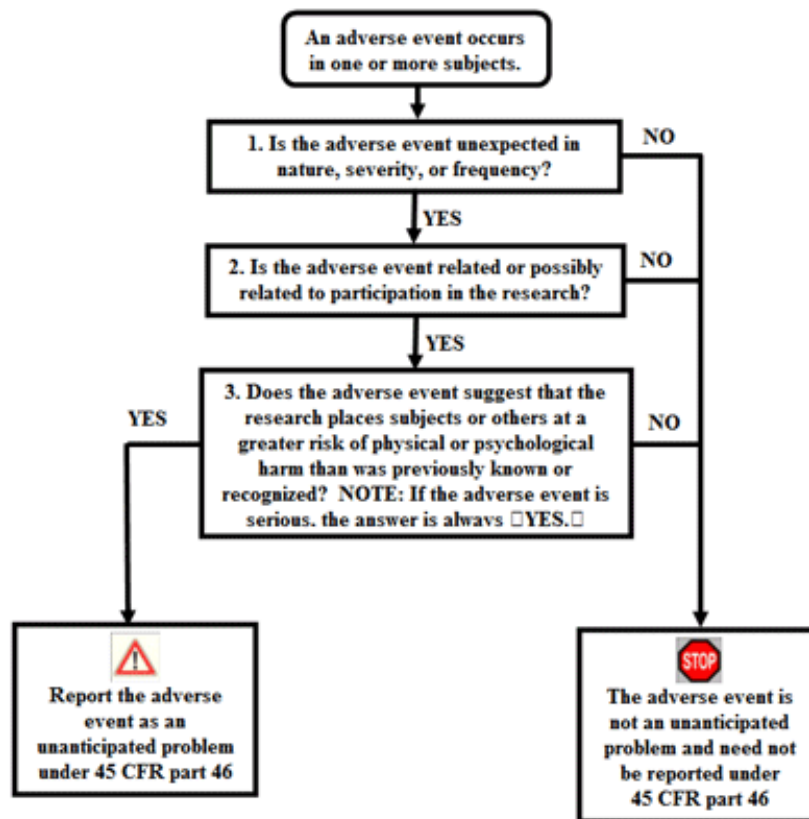
- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (such as tendon rupture, progressive multifocal leukoencephalopathy)

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- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (for example, a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). The FDA recommends that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. The FDA recommends that a discussion of the divergence from the expected specificity or severity accompany the report.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). The FDA recommends that a discussion of the divergence from the expected rate accompany the report.
- Any other AE or safety finding (such as that based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. The FDA recommends that an explanation of the conclusion accompany the report.

Is an Adverse Event an Unanticipated Problem that Must Be Reported?

<http://www.hhs.gov/ohrp/policy/advevntguid.html>



### Investigator Reporting of Unanticipated Problems to the IRB

Events that the investigator believes might meet the definition of UPX (see above) must be reported to the IRB. The method for submitting a UPX report is through the Reportable Event application in the iStar system.

External Adverse Events which are Unexpected, Serious AND suggest that the research places subjects or others at greater risk than was previously recognized, and Related to the Research Intervention will be reported to the IRB within 30 working days of their receipt by the investigator.

The investigator's evaluation of the event is critical. Events that do not meet the definition of unanticipated problems involving risks to subjects or others do not have to

be submitted to the IRB. If submitted, events that do not meet the UPX definition are auto-acknowledged and filed electronically.

**Report contents must include:**

- A detailed description of the event, incident, experience, and or outcome and
- A description of corrective actions that have been taken or are proposed in response to the possible UPX

**Time frame for reporting to the IRB:**

UPXs should be reported to the IRB as soon as possible, but not later than 10 working days after the investigator becomes aware of the event.

For sponsored research, the terms of the contract may define a shorter reporting timeframe.

### 20.4 Adverse Device Effects

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

UADEs must be reported to the IRB through the Reportable Event application in the iStar system.

**Report contents must include:**

- A detailed description of the event, incident, experience, and or outcome
- A description of corrective actions that have been taken or are proposed in response to the possible UADE.

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Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the reporting of unanticipated problems.



### PART II – IRB AND INSTITUTIONAL PERSPECTIVE

## 20.5 IRB Procedure for Handling Reports of Adverse Events

Adverse events may be either internal or external. **Internal Adverse Events** are events experienced by subjects enrolled by USC investigators. **External Adverse Events** are events experienced by subjects enrolled at non-USC Institutions.

Adverse Event reports are submitted by researchers through the iStar system. When the criteria for IRB Chair/Designee review is met\*, the adverse event report is automatically routed to an IRB Chair or Designee. When the criteria for IRB Chair/Designee review are not met, the report is auto-acknowledged by the iStar system. Auto-acknowledged reports are “electronically filed” and are not reviewed by the IRB Chair/Designee.

### IRB Chair / Designee Review

The IRB Chair/Designee reviews all adverse event reports when the reportable event application indicates the event is (all criteria below must apply):

- Unexpected
- Reasonably related (definitely, probably, or possibly)
- Suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized
- Serious

The IRB Chair / Designee reviews the application and either:

- **Acknowledges the Adverse Event**

If the Chair/Designee determines the event does **not** affect the risk/benefit ratio, study protocol, or informed consent, he or she will issue an IRB acknowledgment letter.

- **Forwards the Adverse Event to Full Board for Review**

If the Chair/Designee determines the event affects the risk/benefit ratio, study protocol, or informed consent, or is unsure of a determination, the Chair/Designee

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forwards the report to the Full Board for review. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/Designee may immediately halt further enrollment and/or suspend activities for currently enrolled subjects.

When Full Board review is required, the IRB staff assigns the item to the next Full Board agenda. All board members have access to:

- The adverse event reports
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable
- Any attached supplemental material submitted with the report
- An amendment request, if applicable
- The current IRB approved application, which may include the informed consent documents, sponsor's protocol, investigator's brochure and any other pertinent materials such as advertisements or questionnaires

### IRB Committee Review

The Full Board reviews adverse event reports that were previously evaluated and forwarded from the IRB Chair/Designee. The Full Board reviews the adverse event report and any supporting documents and considers the following actions:

- Accept the report with no changes
- Accept the report with changes to the risk/benefit ratio, the protocol, or the informed consent documents
- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consent of all subjects with the new information
- Defer the reportable event if significant modifications directly related to the approval criteria at 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by a convened IRB.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110) or are explicit changes verifiable by the Chair and/or IRB designee

- Request further information from the investigator or the DSMB
- Increase the frequency of continuing review
- Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor
- Halt enrollment pending receipt of further information
- Determine that the adverse event is an unanticipated problem involving risks to subjects or others and report findings as appropriate depending on the nature of the event
- Suspend any of the following activities:
  - Screening and enrollment
  - Recruitment
  - Intervention and interaction
  - Follow up activities
- Terminate IRB approval of the study according to IRB policy
- Consider whether the event represents serious or continuing noncompliance

### **20.6 IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others (UPX)**

Unanticipated problem reports may come to the IRB through iStar or “offline” from subjects, study staff, or others. Unanticipated problem reports from researchers are submitted through the iStar system. The iStar system either forwards the report to an IRB Chair or Designee for review, or auto-acknowledges the report. When the criteria for IRB review is met the unanticipated problem report is automatically routed to an IRB Chair/Designee. If the reviewer determines the event meets the criteria of a UPX, the event is forwarded to the Full Board for review and verification. The Full Board determines whether proposed changes to the protocol, consent, or other corrective actions are required. Once a UPX determination is made by the Full Board, the UPX will be reported to the appropriate entities according to the reporting policy. (For additional

information, refer to [Section 9.8](#) and [Section 7.14](#). The determination will be documented in the meeting minutes. When the criteria for IRB review are not met, the unanticipated problem report is auto-acknowledged by the iStar system. Auto-acknowledged reports are “electronically filed” and are not reviewed by the IRB Chair/Designee.

### IRB Chair / Designee Review

The IRB Chair/Designee reviews unanticipated problem reports when the reportable event application indicates the event is (all criteria below must apply):

- Unexpected
- Reasonably related (definitely, probably, or possibly)
- Suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized

The IRB Chair/Designee reviews the application and either:

- **Acknowledges the Unanticipated Problem**

If the Chair/Designee determines the reported event does **not** meet the definition of a UPX (also refer to [Section 9.8 – Unanticipated Problems Involving Risk to Subjects or Others](#)), and/or the event does **not** affect the risk/benefit ratio, study protocol or informed consent, he or she will issue an IRB acknowledgment letter.

- **Forwards the Unanticipated Problem to the Full Board for Review**

If the Chair/Designee determines the report is a **possible** UPX, and/or the event affects the risk/benefit ratio, study protocol, or informed consent, or is unsure of a determination, the Chair/Designee forwards the report to the Full Board for committee review. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the Full Board, the Chair/Designee may immediately halt further enrollment and/or suspend activities for currently enrolled subjects. At the same time, the IRB staff assigns the item to the Full Board agenda.

When the report is forwarded to the Full Board, all board members have access to:

- The report of unanticipated problem
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable

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- Any attached supplemental materials submitted with the report
- An amendment request (if there is one)
- The current IRB approved application, which includes (if applicable) the informed consent documents, sponsor's protocol, and investigator's brochure
- Any other pertinent materials such as advertisements or questionnaires

### IRB Committee Review

The Full Board IRB reviews unanticipated problem reports that were previously reviewed by the IRB Chair/Designee. The Full Board makes the final determination as to whether the event meets the definition of a UPX (unexpected, related or possibly related, and suggests that the research places subjects or others at a greater risk of harm than was previously recognized). The Full Board considers the following actions:

- Accept the report with no changes
- Accept the report with changes to the risk/benefit ratio, the protocol, or the informed consent documents
- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consenting all subjects with the new information
- Defer the reportable event if significant modifications directly related to the approval criteria 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by the Full Board.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the Chair and/or IRB designee
- Request further information from the investigator and/or the DSMB
- Increase the frequency of continuing review
- Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor
- Halt enrollment pending receipt of further information

- Report findings as appropriate depending on the nature of the event
- Suspend any or all of the following activities:
  - Screening and enrollment
  - Recruitment
  - Intervention and interaction
  - Follow up activities
- Terminate IRB approval of the study according to IRB policy
- Consider whether the event represents serious and/or continuing noncompliance

### 20.7 IRB Reporting of Adverse Events that are Unanticipated Problems

When applicable, the IRB must report adverse events that are unanticipated problems to:

- OHRP (if federally funded)
- FDA (if subject to FDA regulations)
- Sponsor
- Funding agency (if federal agency)
- Institutional Official
- Principal Investigator
- Department Chair / Director / Principal Investigator's supervisor
- Office of Compliance
- Department of Contracts and Grants
- Other institutional committees (such as Institutional Biosafety Committee)

When the investigator provides documentation that the appropriate federal agency (-ies) and/or study sponsor have already been notified of the event, the IRB will not submit a duplicate report.

## 20.8 Procedure for Handling Reports of Alleged Noncompliance

Noncompliance is a generic term that is used to describe behavior that is not expected or acceptable and may or may not be intentional. Noncompliance may require action by the IRB or the Institution. The following definitions are provided to help with this determination.

### *Definitions Related to Noncompliance*

<b>Noncompliance</b>	Failure to follow federal, state or local regulations governing human research, requirements or determinations of the IRB, or institutional policies. This definition may include action of any University employee or agent, such as investigators, research staff, IRB members, IRB staff, employees, or Institutional Officials.
<b>Serious Noncompliance</b>	An action or omission by an individual (investigator, research staff, IRB member, IRB staff, employee, or Institutional Official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject or others.
<b>Continuing Noncompliance</b>	A pattern of repeated actions or omissions by an individual (investigator, research staff, IRB member, IRB staff, employee, or Institutional Official) that 1) indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP; 2) if allowed to continue could reasonably be expected to develop into serious noncompliance; or 3) recurs after a report of the activity has been evaluated and corrective action has been mandated.

Reports of alleged noncompliance or inappropriate involvement of human subjects in research may come to the attention of the IRB from different sources and by various means. For example, alleged noncompliance may come from an IRB member, an investigator, a subject or their family members, institutional personnel, institutional committees, the Clinical Trials Unit (CTU), the USC Office of Compliance, the media, anonymous sources, or the public. All reports of alleged noncompliance or inappropriate involvement of humans in research are investigated by OPRS, IRB, or both, when appropriate.

Allegations of noncompliance are different from and not considered protocol deviations that occur during the course of clinical research. Very rarely, a protocol deviation may be

considered noncompliance when the deviation compromises the rights and welfare of subjects.

When investigating allegations of noncompliance, the process should include:

- Assuring the safety of human participants
- Developing action plans to prevent reoccurrence, and promote future compliance
- Educating research staff on federal guidelines, regulations, and USC IRB policy
- Reporting serious or continuing noncompliance

### Handling Reports of Noncompliance

Reports of IRB or institutional noncompliance will be dealt with on a case-by-case basis.

#### IRB Review

When the IRB receives a verbal or written report of alleged noncompliance, a preliminary review is conducted and forwarded to the IRB Chair. The materials the IRB Chair reviews to make the determination of serious and/or continuing noncompliance may include a description of the allegation, the entire research file, medical/research charts, interviews with research personnel/PI, and any subject complaints. If the IRB Chair determines the allegation has no merit, the matter will be closed.

If the Chair determines there is merit the matter is scheduled for review by the Full Board.

If more information is needed, the Chair requests an investigation by the IRB staff. The investigator is notified in writing of the directed investigation (audit). The completed audit report is presented to the IRB Chair and reviewed at the next Full Board meeting.

The IRB staff prepares the following documents for Full Board review:

Audit report (investigation report)

- Notification of noncompliance, if applicable
- Pertinent IRB correspondence (such as IRB applications, IRB approval letters, IRB approved informed consent)

The IRB committee reviews the materials at a convened meeting. The discussion, actions, and determinations are noted in the minutes. Upon review, the IRB determines:



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- There is noncompliance that is neither serious nor continuing. The Full Board will formulate a corrective action plan, forward it to the investigator, and require a response from the investigator
- There is serious or continuing noncompliance. The IRB office will report this determination to appropriate agencies, officials, and sponsors
- There is insufficient information to make a determination. In this case, the board will request additional information to be gathered by the IRB staff and defer a determination to a later convened IRB meeting

The Full Board determines the following **corrective actions**, if applicable:

- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consenting all subjects with the new information
- Defer the report if significant modifications directly related to the approval criteria 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by the Full Board
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the Chair and/or IRB designee
- Verification that subject selection is appropriate
- Observation of the informed consent process by the IRB staff
- An increase in monitoring of the research activity via a data safety monitoring board and continuing evaluation of the site by the staff
- Request a directed audit of targeted areas of concern
- Request a status report after a specified number of subjects receive intervention
- Shorten the continuing review cycle
- Request additional investigator and staff education focused on human research protections given by the IRB staff or using other sources (such as Institutional Biosafety Committee (IBC), Radiation Safety Committee (RSC), OHRP conferences, National Institutes of Health (NIH) tutorial, or human research protection seminars)

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- Require notification to current and/or past subjects, if information about the noncompliance might affect subjects' willingness to continue participation
- Suspend the study
- Terminate the study
- If the event involves research misconduct, the IRB Chair will report this to the Dean of the investigator's school and the USC Scientific Misconduct Committee

### 20.9 Suspension or Termination of IRB Approval

The IRB may suspend or terminate research on any study approved by the IRB when the IRB has an indication that circumstances warrant and there is cause (such as serious and continuing noncompliance, increased or undue risk, or unexpected serious harm to subjects).

Examples of actions that may cause suspensions or terminations include: inappropriate involvement of human subjects in research; impairment of the rights or welfare of participants; serious or continuing noncompliance with federal regulations or IRB policies; and new information indicating increased risk to human participants.

Any IRB suspension or termination of approval will include a statement of reasons for the IRB's action. Suspension or termination that occurs outside of a convened IRB meeting (e.g. as determined by the IRB or IO for subject safety reasons) should be reported to the convened IRB and discussion summarized in the minutes. Any action taken by the IRB to lift the suspension or termination must be documented in the minutes ((45 CFR 46.115(a); 21 CFR 56.115(a)(2)).

There is a regulatory difference between suspensions and terminations. It is:

#### Suspension of IRB Approval for Research Study

A suspension exists when the IRB temporarily or permanently withdraws approval of some or all research activities in a protocol. While suspended, the research remains under the jurisdiction of the IRB.

### Termination of IRB Approval for Research Study

Termination takes place when the IRB permanently withdraws approval of ALL research activities in a protocol. Terminated research is no longer required to undergo continuing review and does not remain under the jurisdiction of the IRB.

### IRB Committee Responsibilities

Before suspending IRB approval, the IRB or individual requesting the suspension must consider whether actions are necessary to protect the rights and welfare of currently enrolled subjects (such as allowing subjects to continue in the research, transferring subjects to other investigators, transferring subjects to physicians who will provide clinical care off the protocol, and monitoring of current or former subjects). The IRB may request an ad hoc review from an independent source with expertise in the type of research being conducted or expertise in the specific area of concern. The IRB may request the development of an education plan and/or the completion of a directed audit by the appropriate IRB staff.

The full IRB reviews the study and determines whether circumstances warrant suspension of IRB approval. Some examples of situations that may warrant suspension are:

- Falsification of study safety data
- Failure to comply with prior conditions imposed in writing by the IRB
- Repeated or deliberate failure to obtain or document informed consent from human subjects, which may include:
  - Repeated or deliberate omission of a description of serious risks of the research intervention when obtaining informed consent
  - Repeated or deliberate failure to provide informed consent in a language understandable to the subject
- Repeated or deliberate failure to comply with conditions placed on the study by the University, IRB, sponsor, FDA, or other governmental agency
- Repeated or deliberate failure to obtain prior review and approval of new protocols and on-going human subjects research by the IRB

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- Repeated or deliberate failure to follow the signed Investigator statement or protocol; for example, by enrolling subjects who do not meet inclusion criteria
- Repeated or deliberate failure to maintain accurate study records or submit required adverse event reports to the IRB
- Repeated or deliberate falsification, fabrication, or concealment of study records; for example, by substituting the results of biological samples from subjects who met the inclusion criteria for samples of subjects who do not meet the inclusion criteria, or by fabricating participants

The Institution may determine that suspensions or terminations associated with a particular study or an investigator are repetitive and warrant action for issues of serious and continuing noncompliance.

### Reinstatement of Suspended Research

Reinstatement of suspended research studies occur after corrective actions are completed to the IRB's satisfaction. The Full Board may approve the study with or without additional restrictions (such as mandating a data and safety monitoring committee to oversee the research at designated intervals, increasing the frequency of IRB review, or observing the consent process).

The convened IRB, IRB Chair, and IRB Vice Chairs are all authorized to suspend or terminate research. If there is an urgent situation requiring suspension or termination of a study, the IRB Chair or Vice Chair may make this determination. If the IRB Chair or Vice Chair terminates or suspends a study, the IRB committee may be notified of the action at the next IRB meeting.

The IRB promptly notifies the investigator, in writing, of all suspensions or terminations of IRB approval. The notification letter includes the following:

- Identifies the suspended or terminated research
- Includes a statement of the reasons for the IRB's action
- Requires the investigator to submit proposed procedures for withdrawal of currently enrolled subjects with consideration of subject rights and welfare. The IRB reviews the proposed procedures. The IRB may transfer this responsibility to another investigator to ensure implementation of these procedures
- Requires the investigator to submit a proposed script or letter notifying all currently enrolled subjects that are impacted by the suspension or termination.

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The IRB reviews the proposed script or letter. If follow up with subjects for safety reasons is permitted/required by the IRB, subjects should be so informed. The IRB may directly contact subjects to effect this notification

- As a condition of ending suspension or termination, the IRB may require oversight by an IRB Director, designee, or other, and/or require the study to be transferred to another USC investigator who will serve as the Principal Investigator. The new investigator will ensure that IRB requirements are being implemented and followed

Investigators who fail to comply with IRB directives or federal or state law or regulations may be subject to administrative and/or legal action by the University.

The iStar system automatically notifies the PI in writing of IRB suspensions.

The IRB staff, USC Office of Compliance, and OPRS staff communicate corrective actions to be taken by the investigator as applicable. The IRB staff completes a directed audit and/or develops an education plan as deemed appropriate by the IRB.

Research activities must cease as specified in the suspension criteria, until the IRB has granted approval for the study to resume. Suspensions are within the authority of the IRB and remain in effect until the investigator complies with all corrective actions required by the IRB.

### **Investigator Responsibilities**

When the USC IRB has suspended, terminated, or reinstated a project, the investigator must notify the sponsor. The investigator is responsible for notifying all affected subjects of the suspension, termination, or reinstatement of the research project (by phone, letter, or in person). The subject letter or script must be submitted by the investigator to the IRB for review and approval. The investigator must continue to report adverse events, unanticipated problems involving risks to subjects or others, and serious or continuing noncompliance with federal regulations to the IRB during the period of suspension or termination.

## **20.10 IRB Reporting Requirements to Federal Agencies, Institutional Committees or Others**

This section describes IRB reporting requirements for unanticipated problems involving risks to subjects or others (UPX), serious or continuing noncompliance, suspensions, and terminations.

The following events will be reported as appropriate to institutional personnel and/or committees in accordance with this policy and procedure:

- Any unanticipated problem involving risks to subjects or others (UPX)
- Any serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB
- Any suspension or termination of IRB approval

Additionally, reporting to the appropriate federal agency will also take place if one of the above events require an action such as, but not limited to:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazard to subjects
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional procedures for monitoring subjects
- Suspension of enrollment of new subjects
- Suspension of research procedures in currently enrolled subjects
- Modification of informed consent procedures to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled subjects

When the investigator provides documentation that the appropriate federal agency(-ies) and/or study sponsor has already been notified of the event, the IRB will not submit a duplicate report.

### Report Contents and Routing of Report

If the report is related to IRB or institutional serious or continuing noncompliance, the report is generated by the Office of Compliance and distributed to the Vice President of Research and the Office for the Protection of Research Subjects.

If the report is related to investigator or research personnel noncompliance, the IRB staff will generate a report of unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspension or terminations. The report is forwarded to the IRB Chair. The report includes the following information:

- Title of the research project and/or grant proposal that was suspended or terminated
- Name of the principal investigator
- The study number assigned by the IRB, and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
- A detailed description of the reason for the suspension or termination
- The actions the Institution is taking or plans to take to address the problem, noncompliance or suspension or termination

### Distribution of Report and Timeline

Reports regarding determinations of investigator or research personnel serious or continuing noncompliance, unanticipated problems involving risks to subjects or others, as well as suspension or termination of IRB approval will be submitted by the IRB Chair or Designee as appropriate, to:

- OHRP, if federally funded
- FDA, when the research is subject to FDA regulations
- DOD (Human Research Protection Official), when research is subject to DOD regulations
- Funding agency, when the research is funded by a federal agency
- Institutional Official (if federally funded or not)
- Principal Investigator

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- Department Chair, institute Director, and/or PI's supervisor
- Department of Contract and Grants (only if the report involves suspension or termination of research or is otherwise determined by the IRB leadership to merit reporting to Contract and Grants)
- Non-federal study sponsor (only if the report involves suspension or termination of research or is otherwise determined by the IRB leadership to merit reporting to the sponsor)
- Leadership of any other institutional committee or entity involved in the oversight of the research (such as IBC, Office of Compliance, OPRS)

Reports are to be distributed to the parties described above within 30 days from the determination that the event is reportable. For more serious incidents, reports may be distributed within days from the time at which the determination is made.

When the investigator provides documentation that the appropriate federal agency(-ies) and/or study sponsor has been notified of the event, the IRB will not submit a duplicate report.

### Record Retention

Copies of all reports made in accordance with this policy and corresponding responses are maintained in the iStar study record indefinitely.



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# Chapter 21

## Data Safety Monitoring (DSM)

The USC IRBs follow the Department of Health and Human Services (HHS) and the U.S. Food & Drug Administration (FDA) regulations regarding the monitoring of research for the safety of human subjects. This chapter describes situations in which a plan for the monitoring of research is required, the roles of Data Safety Monitoring Boards (DSMB) and the relationship between DSMBs and IRBs.

### 21.1 Data Safety Monitoring (DSM)

The IRB criteria for approval, as listed in the FDA and OHRP regulations, requires in part that “when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects” [45 CFR 46.111\[a\]\[6\]](#), [21 CFR 56.111\[a\]\[6\]](#). The IRB is responsible for determining when a study needs ongoing monitoring by a data safety monitoring (DSM) plan or the establishment of a data safety monitoring board to ensure protection for research subjects. However, the USC IRBs do not act as data safety monitoring boards.

The regulations do not discuss data and safety monitoring committees or boards. However, in 1998, the NIH created a requirement for data and safety monitoring boards for some of the studies it funds. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB). The NIH Policy for Data and Safety Monitoring is available at: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

The FDA has created guidance for the establishment and operation of clinical trial data monitoring committees. This policy highlights the FDA guidance. To review the FDA guidance in its entirety, visit the website at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

Every clinical trial conducted at USC must include a plan for data and safety monitoring. Specific plans should be based on:

- The amount of risk involved for participating subjects
- The size and complexity of the clinical trial
- The nature of the investigational agent

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- The study sponsor requirements
- The phase of the clinical trial

DSM plans may be required for non-clinical trials and for studies involving more than minimal risk as determined by the IRB.

During the initial IRB approval process and annual review, the IRB will review all proposed protocols for scientific relevance, protocol completeness, and the presence of an appropriate DSM plan.

Investigators will develop a DSM plan based upon the characteristics of the individual study. Investigators must describe how the study will be monitored for the safety of subjects and for the validity and integrity of the data. Sponsor-investigators who act as both the investigator and the study sponsor for drug/biologic/device studies must perform the sponsor data safety monitoring requirements from FDA, HHS, and the funding agency.

### **Appointment of a Research Monitor for Department of Defense (DOD) Sponsored Research**

The following pertain to the appointment of a research monitor for DOD-sponsored research:

- Required for research involving greater than minimal risk, although IRBs can require a research monitor for a portion of the project or for studies involving no more than minimal risk studies if appropriate
- The independent research monitor must be appointed by name
- The research monitor has the authority to:
  - Stop a research study in progress
  - Remove individuals from study
  - Observe group recruitment
  - Take whatever steps are necessary to protect the safety and well-being of participants

### 21.2 Data Safety Monitoring Board (DSMB)

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuing the study is scientifically and ethically appropriate. DSMB's are also known as Data Monitoring Committees (DMCs) or Data and Safety Monitoring Committees (DSMCs).

#### Factors that Suggest a DSMB Is Needed

- A large study population
- Multiple study sites (it is more difficult to recognize a pattern of increased or unusual problems when one site enrolls only a small percentage of the study population)
- The study is blinded
- The study employs high-risk interventions that may include highly toxic therapies or dangerous procedures, expected high rates of morbidity or mortality in the study population, or high chance of early termination of the study
- The study includes vulnerable populations, such as minors, prisoners, and/or pregnant women

#### FDA Guidance on Data and Safety Monitoring Boards, Committees, and Plans

FDA regulations (21 CFR 56) specifically require a Data Monitoring Committee (DMC) only for research conducted in emergency settings with an exception from informed consent requirements (21 CFR 50.24). However, all clinical trials require safety monitoring, and sponsors of trials evaluating new drugs, biologics, and devices are required to ensure proper monitoring of the trial.

FDA guidance defines a DMC as a group of individuals with pertinent expertise that regularly reviews accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of study subjects as well as the continuing validity and scientific merit of the trial. The FDA recommends that sponsors establish a DMC in studies where safety concerns may be unusually high, such as when:

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- There are *a priori* reasons for a particular safety concern; for example, the procedure for administering the treatment is particularly invasive
- There is prior information suggesting the possibility of serious toxicity with the study treatment
- The study is being performed in a potentially fragile population such as children, pregnant women, the elderly, or other vulnerable populations such as those who are terminally ill or of diminished mental capacity
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint
- The study is large, of long duration, and multi-center
- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion

### Data Monitoring Committee for Investigator-Initiated Research

The FDA recommends that when the investigator is also the product manufacturer or IND/IDE sponsor and thereby subject to potentially strong influences related to financial and/or intellectual incentives, a DMC would provide additional, independent oversight that would enhance safety of study subjects and the credibility of the product development. DMCs should be considered in such settings.

### IRBs and DMCs

In order to determine that risks are being minimized “by using procedures that are consistent with sound research design”, the IRB may appropriately ask for information about the approach to trial monitoring, including the statistical basis for early termination (when relevant) and what steps the sponsor is taking to minimize risks to subjects.

Since multi-site clinical trials generally have many IRBs and only one DMC, the DMC often has more information about the data, including interim efficacy and safety data than any single IRB. IRBs may want to appropriately take advantage of this situation and request information about the latest meeting and recommendations from the DMCs, even when those reports and recommendations show that no problems have been identified.

### DMC Charters

DMCs typically operate under a written charter that includes their operating procedures. These procedures generally include the schedule and format of meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC meetings, procedures for assessing conflicts of interest of the DMC members, the method of providing interim reports to the DMC, and other issues relevant to committee operations.

Frequency of DMC meetings may depend on the expected rate of accrual and event occurrence at the time the trial is designed as well as the perceived risk of the experimental or control interventions. Annual meetings maybe adequate for some studies; other trials will require more frequent review. The study protocol will generally describe the schedule of interim analyses or other considerations that will determine meetings.

The IRB may ask for the DMC charter during initial review of the study.

### Independence of the DMC

Independence of the DMC will depend upon the relations of its members to those sponsoring, organizing, conducting, and regulating the trial. Independence is greatest when members have no involvement in the design and/or conduct of the trial except through their role on the DMC, and have no financial or other important connection to the sponsor (other than compensation for serving on the DMC). However, DMCs are rarely totally independent since the sponsor usually selects members, gives them their charge, and pays them for their services.

## 21.3 The Relationship Between DSMBs and IRBs

The National Institutes of Health (NIH) explicitly identifies required communication that must occur between DSMBs and IRBs when multicenter trials are supported by the NIH (For details see: [https://humansubjects.nih.gov/data\\_safety](https://humansubjects.nih.gov/data_safety)). Generally, the DSMB provides feedback at regular and defined intervals to IRBs. After each meeting of the DSMB, the DSMB Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB

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members' conclusions with respect to progress or need for modification of the protocol. Investigators are required to transmit the report to their local IRBs.

For studies sponsored by National Cancer Institute (NCI) see safety monitoring guidelines, visit: <https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf>

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## Chapter 22

# Complaints Regarding Human Subjects Research

A well run and well documented HSPP has mechanisms in place to receive and address complaints from any concerned party. This chapter contains information about participant complaints, undue influence, and the IRB/HSPP.

## 22.1 Handling Complaints Regarding Human Subjects Research

### Participant Complaints

A participant complaint is an expression of dissatisfaction by the participant (or his/her representative) that may or may not involve a breach in human subjects rights or research ethics. Participants may choose to report complaints to the study team or to a third party. Therefore, it is important that during the consent process, subjects receive consent forms and information sheets that include investigator and IRB contact information so that participants have resources to ask questions about the study and report complaints.

At USC, participants can also address their complaints to the Office for the Protection of Research Subjects (OPRS) and the Office of Compliance (OOC).

### OPRS Resources for Participant Complaints

The OPRS website contains contact information for OPRS, IRBs, and OOC, a webpage specific to participant complaints and a brochure for participants considering study participation with contact information for questions or complaints.

- OPRS and IRB contact information:  
<http://oprs.usc.edu/about/complaints/>
- Participant brochure:  
[Should I Participate in Research?](#)

### OOO Resources for Participant Complaints

The USC Office of Compliance Help and Hotline can be utilized by participants to report complaints or ask questions about applicable laws, regulations and USC policies. Complaints may be made anonymously by calling the OOC Help and Hotline at (213)740-2500.

- [OOO Contact Information](#)
- [OOO Help and Hotline](#)

At USC, subject complaints should be reported by the study team in iStar using the “Participant Complaint” form in the “Reportable Events” application. The report should be specific and include: date of the complaint, event description, relation to the study, determination of whether the complaint involves increased risk to study participants, explanation of how a similar event will be prevented in the future and supporting documentation if applicable. Alternatively, the study team can choose to contact the IRB directly to discuss the participant complaint. Additionally, complaints reported to OPRS, OOC or third parties will be subsequently reported to the IRB. When the IRB receives a participant complaint, the IRB staff or Director will be responsible for documenting the complaint in iStar.

Once a subject complaint is received, the IRB, along with OPRS or OOC as applicable, will attempt to substantiate the complaint in a timely manner. This process involves reviewing the study in which the subject is enrolled to ensure that the study has received and maintains active IRB approval and ensure compliance with pertinent federal and state regulations. The IRB office may contact the Principal Investigator (PI) and/or research staff for additional information to assist with the validation and/or dismissal of the complaint. Once all the information is received, the IRB will determine if any further action is necessary. The IRB will then provide written correspondence to the subject and PI with their determination and justification for actions taken. The determination and outcome of the complaint will be documented in iStar by the IRB.

If the IRB/OPRS office suspects there may be potential non-compliance, the IRB will initiate the process as outlined in the policy on handling allegations of non-compliance. Refer to [Section 20.8 – Procedure for Handling Reports of Noncompliance](#) for more information.

### Complaints Regarding Undue Influence

Undue influence is a situation in which one person takes advantage of a position of power over another person. Any IRB staff member, IRB member, or other individual involved in the review of research, who believes they have been the target of undue influence by an investigator or other individual should report the incident to the IRB Director, Chair, or call the Office of the Compliance Help and Hotline **(213)740-2500 or (800) 348-7454**.

If the IRB is contacted, the Director or Chair will attempt to get all available information and, if warranted, forward the validated allegation to the Office of Compliance, where corrective action will be undertaken.

### Complaints Regarding the IRB or HSPP

Subjects/participants, researchers, IRB members, and others who have human subjects research related complaints, concerns, recommendations, or reports of violations are encouraged to contact one of the following offices listed below. Aspects of the HSPP unrelated to the IRB may also be directed to these offices. All inquiries are taken seriously and will be directed to the appropriate personnel. When a complaint, concern, recommendation, or report of violation made to any one of the offices listed below reveals the need to consider modifying any aspect of USC's Human Subjects Research Protection Program, due consideration will be given and changes made as appropriate.

Complaints regarding the IRB or aspects of the non-IRB HSPP should be made to the nearest organization entity independent of the IRB. This could be the OPRS, Office of Compliance, or the Vice President of Research (Institutional Official). Attempts to get adequate information to validate the circumstances of the complaint will be sought by one or all of these entities. The contact information for these entities is found at <http://oprs.usc.edu/about/complaints/>. Complaints may be made anonymously by calling the OOC Help and Hotline at (213)740-2500 or (800) 348-7454.

# Appendices

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# Appendices

## A. Federalwide Assurances (FWAs)

The University of Southern California maintains assurances of compliance with the Office for Human Research Protections (OHRP) to comply with the requirements set forth in [45 CFR Part 46](#), as well as the [Terms of Assurance](#). USC's assurance can be accessed at: <https://oprs.usc.edu/irb-review/fwa-and-irb-registration-numbers/>

## B. IRB Reviewer Checklists / Guidelines

The checklists provide insight into how applications are initially assessed by the IRB. Topics include new applications, informed consent, research with pregnant women, research with prisoners, research with children and more. The checklists can be accessed at: <https://oprs.usc.edu/irb-review/checklists-for-irb-review/>

## C. IRB Reliance Agreements

USC has established reliance agreements to simplify the IRB review process for projects taking place between USC and partner sites. Under the Memoranda of Understanding (MOU), IRB Authorization Agreement (IRBAA), Master Reliance Agreement (MRA), Collaborative Review Agreement (CRA), and Ceded Review -one Institution will give the responsibility of the IRB review process to another Institution that will provide the IRB review and approval, and typically ongoing oversight. USC's agreements with CHLA, Hebrew Union College, Rancho Los Amigos, Rand Cooperation, and many others may be found at [IRB Review Agreements](#).

## D. Glossary of Terms Used in Human Subjects Research

A compilation of common terms used in healthcare and research is available at: [Ohio State University – Human Research Protections Program Glossary](#)

## E. Requirements for Department of Defense (DOD) Supported Research and Reviewer Checklist

Research supported by the Department of Defense (DOD) is subject to additional IRB requirements/documentation depending on study specifics. DOD IRB Checklist and

summary requirements are available at: <https://oprs.usc.edu/irb-review/checklists-for-irb-review/>

### **F. IRB Forms and Templates**

Methods of consent and documentation will vary according to the level of review and nature of the research. Templates containing the required elements of consent can be accessed at the OPRS website. Search “Forms and Templates”: <https://oprs.usc.edu>

### **G. USC Human Subjects Research Booklets**

The USC Human Subjects Protection Program has developed booklets available to users online or in hard copy by request. Topics and titles include Responsible Conduct of Research, Making Sense of Human Subjects Research, Informed Consent and More. The booklets are available at: <https://oprs.usc.edu/?s=Human+Subjects+Research+Booklets>